

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



HLA Allele Frequencies in Pediatric and Adolescent Multiple Sclerosis Patients

Maria Anagnostouli and Maria Gontika

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.81645>

Abstract

Early-onset (pediatric and adolescent) multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disorder of the central nervous system, which accounts for 3–5% of all MS cases. The major histocompatibility complex (MHC) with its polymorphisms has been the genetic locus with the most robust association with adult MS, since its first discovery in the 1970s. Nowadays, human leukocyte antigen (HLA) typing studies and genome-wide association studies (GWAS) have tried to provide insight into the genetics of early-onset MS and their role in disease diagnosis, prognosis, and therapeutic decision-making. Fundamental genetic similarities have emerged, supporting the assumption that MS shares similar genetic variants and biological processes in all age groups. In this chapter, we considered it useful to collect all the available data concerning the HLA distribution in early-onset MS, given the absence of a review paper with such an approach. We additionally aimed toward the summarization of the association of the HLA frequencies in early-onset MS and the main acquired demyelinating disorders that are considered in differential diagnosis of early-onset MS, like ADEM, NMO/NMOSD, and anti-MOG encephalopathy, for further understanding and current or future research in this promising field.

Keywords: multiple sclerosis, pediatric, early onset, human leukocyte antigens, immunogenetics, therapy, precision medicine

1. Introduction

Early-onset (pediatric and adolescent) multiple sclerosis (MS), which accounts approximately for 3–5% of all MS cases worldwide, has recently aroused the interest of the scientific community regarding its underlying pathogenetic mechanisms, both autoimmune demyelination and neurodegeneration of the central nervous system (CNS) [1–3]. Additionally, in this

specific age, other acquired demyelinating diseases are in the MS differential diagnosis of everyday practice, like ADEM, anti-MOG encephalopathy, and optic neuritis [4]. Recently, anti-NMO, anti-MOG, and other autoantibodies have been established as strong biomarkers of the previously referred newly emerged clinical entities or a key element of classical demyelinating diseases, like MS, especially of early onset [5, 6].

Nevertheless, for four decades now, the HLA alleles have been globally recognized as the core genetic (risk or protective) component in adult MS. Since the early 1970s, the major histocompatibility complex (MHC) with its polymorphisms on chromosome 6p21.3 [7, 8] has been the genetic locus with the most robust association with MS. In specific, DRB1*1501 (split of DR2), along with DRB1*0301 and DRB1*1301, has been found to confer risk for MS, while HLA-A*0201 protection against MS [9]. Genome-wide association studies (GWAS) regarding early-onset MS are still ongoing, in contrast with large-scale cohorts of adult-onset MS patients. However, single nucleotide polymorphisms (SNPs) of more modest effect have been detected that influence the risk of both adult- and early-onset MS, equalizing the genetic burden of these age groups [10–12]. The HLA alleles that have been studied in early-onset MS concern mainly the class II DRB1* and DQB1* loci, although DPB1* alleles confer susceptibility in adult-onset MS as well [13]. Thus, HLA immunogenetics in early-onset MS apart from the lower number of worldwide studies needs an extension to the whole HLA class I and class II systems, given the increased role that was in MS risk and MS association with vitamin D, body mass index (BMI), hormones, estrogen receptor, gender, EDSS score, disease course, MRI findings, cognitive status, and most importantly neutralizing antibody formation and response to treatment [8, 14–18].

In this chapter, we present the available data concerning the HLA distribution in early-onset MS, in parallel with the other acquired demyelinating diseases, given the increased knowledge that has recently emerged in this promising field. We also aimed to include all this useful data in a workable table.

2. HLA allele distribution in early-onset MS worldwide

Regarding HLA alleles, DRB1*15 association with early-onset MS has been noted by a series of studies [12, 19–22]. In 2000, a study of 286 Norwegian MS patients demonstrated that the HLA-DR2, DQ6 haplotype is negatively correlated with age at diagnosis [23]. Since then, many studies came to show that DRB1*15-positive patients have a significantly earlier age at onset than DRB1*15-negative patients [18, 24–30]. Maslova et al. replicated this testimony in a pure pediatric Russian population in 2000 [31]. An Australian study of 978 patients in 2010 went further to prove that carrying DRB1*15 significantly decreases the age of MS onset by 3.2 years in homozygotes and 1.3 years in heterozygotes [32].

On the other hand, a series of studies pleads against these remarks and claims no correlation of DRB1*15 status and age of disease onset [33–39]. In a Korean population, close linkage of DRB3*02, DRB1*13, and DQB1*03 was also associated with the risk of childhood MS, while DRB1*1501 was not as high as in Western children [40].

	MS	NMO	ADEM
HLA alleles	HLA-DRB1*1501 (Caucasian)	HLA-DRB1*03 (adult Caucasian)	HLA-DRB1*01 and HLA-DRB1*017 (Russian)
	HLA-DRB1*0401 (Caucasian)	HLA-DRB1*0501 (adult Japanese)	HLA-DRB1*1501 and HLA-DRB5*0101 (Korean)
	HLA-DRB3*02, HLA-DRB1*13, and HLA-DQB1*03 (Korean)		HLA-DQB1*0602, HLA-DRB1*1501, and HLA-DRB1*1503 (Brazil)
			HLA-DRB1*16 and HLA-DQB1*05 (Caucasian adult)

MS, multiple sclerosis; ADEM, acute disseminated encephalomyelitis; NMO, neuromyelitis optica.

Table 1. Summary of the available data regarding the HLA allele distribution in early-onset multiple sclerosis, ADEM, and NMO [12, 18–41, 46–49].

A remarkable DRB1-genotyping study in Australia in 2010 declared the first results indicative of the significance of the epistatic interactions at the HLA-DRB1 locus. Carriage of the DRB1*1501 allele alone was not significantly associated with age at disease onset, while the DRB1*0401 allele was associated with a reduced age at onset when combined with DRB1*1501 [41].

Regarding Greece, Anagnostouli et al. in 2003 noticed for the first time the higher frequency of DRB1*1501 in MS patients [42]. In 2011, Kouri et al. [43] observed no significant correlations among DRB1*1501, DQB1*0602, and DQA1*0102 alleles with age at onset, an observation repeated by Anagnostouli et al. in 2014 [20]. Anagnostouli et al. attributed this discrepancy either to a possible parent of origin effect, relying on Ramagopalan et al.’ observation that only maternally transmitted DRB1*15 promotes a lower age of MS [44], or to fluctuations of vitamin D levels among different populations [45]. New findings in this former are the putative predisposing role of DRB1*03 allele and the protective role of the DRB1*16 allele for early-onset MS [20].

While the role of HLA alleles in early-onset MS has been well studied, this is not the case in other young-onset acquired demyelinating diseases, especially acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica (NMO), its main differential diagnoses. In **Table 1**, we summarize the available data regarding the HLA allele distribution in early-onset MS, ADEM, and NMO, and despite the obvious lack of information, the primary results demonstrate clear genetic diversity [12, 18–41, 46–49].

3. Conclusions

The well-established HLA-DRB1*15:01 allele associated with adult-onset MS appears to confer increased susceptibility to early-onset MS too, supporting a fundamental similarity in genetic contribution to MS risk, regardless of age at onset. Regarding whether HLA-DRB1*1501 by itself lowers the age at onset of MS, the results are conflicting and possibly related to both genetic and environmental epistatic mechanisms and in particular those through HLA-DRB1*04. Moreover,

HLA-DRB1*04 also appears to bind with high affinity to myelin oligodendrocyte glycoprotein (MOG) epitopes, whose role in early-onset demyelinating disorders has been widely studied, in both familial MS patients and asymptomatic relatives, indicating that the humoral immune reactivity against MOG is partially under control of certain HLA class II alleles [50–54]. This observation could guide therapy, as HLA-DRB1*0401 allele is associated with greater risk of developing neutralizing antibodies against interferon beta (IFN- β) in adult studies, resulting in poorer therapeutic outcome [55]. Finally, the putative relation of DRB1*03 allele with early-onset MS is also interesting, as this allele has been associated not only with a presumed better MS prognosis but also with NMO [46], a mainly humoral immunological entity.

Accumulating data highlights the role of HLA-genotype and especially HLA-DRB1*1501 in regulating the immune response to a range of environmental factors, modulating the risk of MS appearance. Research has mainly focused on viral infections, especially EBV [56–58], CMV, and HSV-1 [58]. In specific, Epstein–Barr nuclear antigen-1 seropositivity has been associated with an increased risk of MS, while a remote infection with CMV with a lower risk. A strong interaction has been found between HSV-1 status and HLA-DRB1 in predicting MS, as HSV-1 has been associated with an increased risk of MS only in DRB1*15 carriers. Moreover, obesity and higher body mass index (BMI) during adolescence, rather than childhood, seem to be critical in determining MS risk [59], while tobacco smoke exposure and HLA-DRB1*15 interact to increase risk for MS in children diagnosed with monophasic acquired demyelinating syndromes [60]. Finally, as research regarding the role of gut bacteria in the development of central nervous demyelinating disorders robustly expands, possible protective correlations of specific bacteria through interplay with specific HLA alleles emerge in animal models of MS, expanding our knowledge regarding disease pathogenesis [61, 62]. Larger studies in early-onset MS populations are required in order to clarify these possible correlations which may also expand to other HLA alleles, proving the interplay among cellular activity, humoral activity, and environment in MS and their possible impact in therapeutics.

In conclusion, HLA alleles emerge as a primary biomarker in both early- and adult-onset MS, regarding genetic risk, outcome, and differential diagnosis. We strongly believe that larger HLA-genotyping studies regarding early-onset demyelinating disorders are needed, in different ethnic groups, in order to clarify, replicate, and expand the already limited existing results. We also believe that these future studies will aim toward personalized therapeutics and generally precision medicine in early-onset MS patients.

Author details

Maria Anagnostouli^{1,2*} and Maria Gontika¹

*Address all correspondence to: managnost@med.uoa.gr

1 Immunogenetics Laboratory, 1st Dep. of Neurology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

2 Demyelinating Diseases Clinic, 1st Dep. of Neurology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

References

- [1] Renoux C, Vukusic S, Confavreux C. The natural history of multiple sclerosis with childhood onset. *Clinical Neurology and Neurosurgery*. 2008;**110**(9):897-904
- [2] Venkateswaran S, Banwell B. Pediatric multiple sclerosis. *The Neurologist*. 2010;**16**(2): 92-105
- [3] Ferreira ML, Machado MI, Dantas MJ, Moreira AJ, Souza AM. Pediatric multiple sclerosis: Analysis of clinical and epidemiological aspects according to National MS Society consensus 2007. *Arquivos de Neuro-Psiquiatria*. 2008;**66**(3B):665-670
- [4] Hintzen RQ, Dale RC, Neuteboom RF, et al. Pediatric acquired CNS demyelinating syndromes: Features associated with multiple sclerosis. *Neurology*. 2016;**87**(9 Suppl 2): S67-S73
- [5] Chitnis T, Ness J, Krupp L, et al. Clinical features of neuromyelitis optica in children: US network of pediatric MS centers report. *Neurology*. 2016;**86**(3):245-252
- [6] Hennes EM, Baumann M, Lechner C, et al. MOG Spectrum disorders and role of MOG-antibodies in clinical practice. *Neuropediatrics*. 2018;**49**(1):3-11
- [7] Ramagopalan SV, Dymnt DA, Ebers GC. Genetic epidemiology: The use of old and new tools for multiple sclerosis. *Trends in Neurosciences*. 2008;**31**:645-652
- [8] Katsavos S, Anagnostouli M. Biomarkers in multiple sclerosis: An up-to-date overview. *Multiple Sclerosis International*. 2013;**2013**:340508
- [9] International Multiple Sclerosis Genetics Consortium; Welcome Trust Case Control Consortium 2, Sawcer S, Hellenthal G, Pirinen M, Spencer CC, et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature*. 2011;**476**:214-219
- [10] Disanto G, Ramagopalan SV. Similar genetics of adult and pediatric MS: Age is just a number. *Neurology*. 2013;**81**(23):1974-1975
- [11] Graves JS, Barcellos LF, Simpson S, et al. The multiple sclerosis risk allele within the AHI1 gene is associated with relapses in children and adults. *Multiple Sclerosis Related Disorders*. 2018;**19**:161-165
- [12] Gianfrancesco MA, Stridh P, Shao X, et al. Genetic risk factors for pediatric-onset multiple sclerosis. *Multiple Sclerosis*. 2017;**1**:1352458517733551
- [13] Patsopoulos NA, Barcellos LF, Hintzen RQ, et al. Fine-mapping the genetic association of the major histocompatibility complex in multiple sclerosis: HLA and non-HLA effects. *PLoS Genetics*. 2013;**9**(11):e1003926
- [14] Sintzel MB, Rametta M, Reder AT, et al. Vitamin D and multiple sclerosis: A comprehensive review. *Neurology and Therapy*. 2018;**7**(1):59-85
- [15] Hedström AK, Lima Bomfim I, Barcellos L, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. *Neurology*. 2014;**82**(10):865-872

- [16] Kikuchi S, Fukazawa T, Niino M, et al. Estrogen receptor gene polymorphism and multiple sclerosis in Japanese patients: Interaction with HLA-DRB1*1501 and disease modulation. *Journal of Neuroimmunology*. 2002;**128**(1-2):77-81
- [17] Katsavos S, Artemiadis A, Davaki P, et al. Familial multiple sclerosis in Greece: Distinct clinical and imaging characteristics in comparison with the sporadic disease. *Clinical Neurology and Neurosurgery*. 2018;**173**:144-149
- [18] Okuda DT, Srinivasan R, Oksenberg JR, et al. Genotype-phenotype correlations in multiple sclerosis: HLA genes influence disease severity inferred by 1HMR spectroscopy and MRI measures. *Brain*. 2009;**132**(Pt 1):250-259
- [19] Stamatelos P, Anagnostouli M. HLA-genotype in multiple sclerosis: The role in disease onset, clinical course, cognitive status and response to treatment: A clear step towards personalized therapeutics. *Immunogenetics Open Access*. 2017;**2**:116. (review in press)
- [20] Anagnostouli M, Manouseli A, Artemiadis A, et al. HLA-DRB1* allele frequencies in pediatric, adolescent and adult-onset multiple sclerosis patients, in a Hellenic sample. Evidence for new and established associations. *Multiple Sclerosis Journal*. 2014;**1**:1
- [21] Banwell B, Bar-Or A, Arnold DL, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: A prospective national cohort study. *Lancet Neurology*. 2011;**10**(5):436-445
- [22] Disanto G, Magalhaes S, Handel AE, et al. HLA-DRB1 confers increased risk of pediatric-onset MS in children with acquired demyelination. *Neurology*. 2011;**76**(9):781-786
- [23] Celius EG, Harbo HF, Egeland T, et al. Sex and age at diagnosis are correlated with the HLA-DR2, DQ6 haplotype in multiple sclerosis. *Journal of the Neurological Sciences*. 2000;**178**(2):132-135
- [24] Masterman T, Ligers A, Olsson T, et al. HLA-DR15 is associated with lower age at onset in multiple sclerosis. *Annals of Neurology*. 2000;**48**(2):211-219
- [25] Hensiek AE, Sawcer SJ, Feakes R, et al. HLA-DR 15 is associated with female sex and younger age at diagnosis in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2002;**72**(2):184-187
- [26] Weatherby SJ, Thomson W, Pepper L, et al. HLA-DRB1 and disease outcome in multiple sclerosis. *Journal of Neurology*. 2001;**248**(4):304-310
- [27] Smestad C, Brynedal B, Jonasdottir G, et al. The impact of HLA-A and -DRB1 on age at onset, disease course and severity in Scandinavian multiple sclerosis patients. *European Journal of Neurology*. 2007;**14**(8):835-840
- [28] Imrell K, Greiner E, Hillert J, Masterman T. HLA-DRB115 and cerebrospinal-fluid-specific oligoclonal immunoglobulin G bands lower age at attainment of important disease milestones in multiple sclerosis. *Journal of Neuroimmunology*. 2009;**210**(1-2):128-130
- [29] Balnyte R, Rastenyte D, Vaitkus A, et al. The importance of HLA DRB1 gene allele to clinical features and disability in patients with multiple sclerosis in Lithuania. *BMC Neurology*. 2013;**13**:77

- [30] Al-Shammri S, Nelson RF, Al-Muzairi I, Akanji AO. HLA determinants of susceptibility to multiple sclerosis in an Arabian gulf population. *Multiple Sclerosis*. 2004;**10**(4):381-386
- [31] Maslova OI, Bykova OV, Guseva MR, et al. Multiple sclerosis with early onset: Pathogenesis, clinical characteristics, possibilities in the treatment of its pathogenesis. *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova*. 2002;(Suppl):46-51
- [32] Van der Walt A, Stankovich J, Bahlo M, et al. Heterogeneity at the HLA-DRB1 allelic variation locus does not influence multiple sclerosis disease severity, brain atrophy or cognition. *Multiple Sclerosis*. 2011;**17**(3):344-352
- [33] Villoslada P, Barcellos LF, Rio J, et al. The HLA locus and multiple sclerosis in Spain. Role in disease susceptibility, clinical course and response to interferon beta. *Journal of Neuroimmunology*. 2002;**130**(1-2):194-201
- [34] Barcellos LF, Sawcer S, Ramsay PP, et al. Heterogeneity at the HLA-DRB1 locus and risk for multiple sclerosis. *Human Molecular Genetics*. 2006;**15**(18):2813-2824
- [35] Barcellos LF, Oksenberg JR, Begovich AB, et al. HLA-DR2 dose effect on susceptibility to multiple sclerosis and influence on disease course. *American Journal of Human Genetics*. 2003;**72**(3):710-716
- [36] Silva AM, Pereira C, Bettencourt A, et al. The role of HLA-DRB1 alleles on susceptibility and outcome of a Portuguese multiple sclerosis population. *Journal of the Neurological Sciences*. 2007;**258**(1-2):69-74
- [37] Ouadghiri S, El Alaoui Toussi K, Brick C, et al. Genetic factors and multiple sclerosis in the Moroccan population: A role for HLA class II. *Pathologie Biologie*. 2013;**61**(6):259-263
- [38] Ballerini C, Guerini FR, Rombolà G, et al. HLA-multiple sclerosis association in continental Italy and correlation with disease prevalence in Europe. *Journal of Neuroimmunology*. 2004;**150**(1-2):178-185
- [39] Boiko AN, Gusev EI, Sudomoina MA, et al. Association and linkage of juvenile MS with HLA-DR2(15) in Russians. *Neurology*. 2002;**58**(4):658-660
- [40] Oh HH, Kwon SH, Kim CW, et al. Molecular analysis of HLA class II-associated susceptibility to neuroinflammatory diseases in Korean children. *Journal of Korean Medical Science*. 2004;**19**:426-430
- [41] Wu JS, Qiu W, Castley A, et al. Modifying effects of HLA-DRB1 allele interactions on age at onset of multiple sclerosis in Western Australia. *Multiple Sclerosis*. 2010;**16**(1):15-20
- [42] Bozikas VP, Anagnostouli MC, Petrikis P, et al. Familial bipolar disorder and multiple sclerosis: A three-generation HLA family study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2003;**27**(5):835-839
- [43] Kouri I, Papakonstantinou S, Bempes V, et al. HLA associations with multiple sclerosis in Greece. *Journal of the Neurological Sciences*. 2011;**308**(1-2):28-31
- [44] Ramagopalan SV, Byrnes JK, Dyment DA, et al. Parent-of-origin of HLA-DRB1*1501 and age of onset of multiple sclerosis. *Journal of Human Genetics*. 2009;**54**(9):547-549

- [45] Ramagopalan SV, Maugeri NJ, Handunnetthi L, et al. Expression of the multiple sclerosis-associated MHC class II allele HLA-DRB1*1501 is regulated by vitamin D. *PLoS Genetics*. 2009;**5**:e1000369
- [46] Gontika M, Anagnostouli M. Human leukocyte antigens immunogenetics of neuromyelitis optica or Devic's disease and the impact on the immunopathogenesis, diagnosis and treatment: A critical review. *Neuroimmunology and Neuroinflammation*. 2014;**1**:44-50
- [47] Imbesi D, Calabrò RS, Gervasi G, et al. Does HLA class II haplotype play a role in adult acute disseminated encephalomyelitis? Preliminary findings from a southern Italy hospital-based study. *Archives Italiennes de Biologie*. 2012;**150**(1):1-4
- [48] Alves-Leon SV, Veluttini-Pimentel ML, Gouveia ME, et al. Acute disseminated encephalomyelitis: Clinical features, HLA DRB1*1501, HLA DRB1*1503, HLA DQA1*0102, HLA DQB1*0602, and HLA DPA1*0301 allelic association study. *Arquivos de Neuro-Psiquiatria*. 2009;**67**(3A):643-651
- [49] Idrissova ZR, Boldyreva MN, Dekonenko EP, et al. Acute disseminated encephalomyelitis in children: Clinical features and HLA-DR linkage. *European Journal of Neurology*. 2003;**10**(5):537-546
- [50] Forsthuber TG, Shive CL, Wienhold W, et al. T cell epitopes of human myelin oligodendrocyte glycoprotein identified in HLA-DR4 (DRB1*0401) transgenic mice are encephalitogenic and are presented by human B cells. *Journal of Immunology*. 2001;**167**(12):7119-7125
- [51] Klehmet J, Shive C, Guardia-Wolff R, et al. T cell epitope spreading to myelin oligodendrocyte glycoprotein in HLA-DR4 transgenic mice during experimental autoimmune encephalomyelitis. *Clinical Immunology*. 2004;**111**(1):53-60
- [52] Khare M, Rodriguez M, David CS. HLA class II transgenic mice authenticate restriction of myelin oligodendrocyte glycoprotein-specific immune response implicated in multiple sclerosis pathogenesis. *International Immunology*. 2003;**15**(4):535-546
- [53] Raddassi K, Kent SC, Yang J, et al. Increased frequencies of myelin oligodendrocyte glycoprotein/MHC class II-binding CD4 cells in patients with multiple sclerosis. *Journal of Immunology*. 2011;**187**(2):1039-1046
- [54] Lutterotti A, Reindl M, Gassner C, et al. Antibody response to myelin oligodendrocyte glycoprotein and myelin basic protein depend on familial background and are partially associated with human leukocyte antigen alleles in multiplex families and sporadic multiple sclerosis. *Journal of Neuroimmunology*. 2002;**131**(1-2):201-207
- [55] Buck D, Cepok S, Hoffmann S, et al. Influence of the HLADRB1 genotype on antibody development to interferon beta in multiple sclerosis. *Archives of Neurology*. 2011;**68**(4):480-487
- [56] Waubant E, Mowry EM, Krupp L, et al. Antibody response to common viruses and human leukocyte antigen-DRB1 in pediatric multiple sclerosis. *Multiple Sclerosis*. 2013;**19**(7):891-895

- [57] Morandi E, Jagessar SA, 't Hart BA, Gran B. EBV infection empowers human B cells for autoimmunity: Role of autophagy and relevance to multiple sclerosis. *Journal of Immunology*. 2017;**199**(2):435-448
- [58] Waubant E, Mowry EM, Krupp L, et al. Common viruses associated with lower pediatric multiple sclerosis risk. *Neurology*. 2011;**76**(23):1989-1995
- [59] Hedström AK, Olsson T, Alfredsson L. Body mass index during adolescence, rather than childhood, is critical in determining MS risk. *Multiple Sclerosis*. 2016;**22**(7):878-883
- [60] Lavery AM, Collins BN, Waldman AT, et al. The contribution of secondhand tobacco smoke exposure to pediatric multiple sclerosis risk. *Multiple Sclerosis*. 2018;**1**:1352458518757089
- [61] Mangalam A, Shahi SK, Luckey D, et al. Human gut-derived commensal bacteria suppress CNS inflammatory and demyelinating disease. *Cell Reports*. 2017;**20**(6):1269-1277
- [62] Lerner A, Matthias T. Rheumatoid arthritis-celiac disease relationship: Joints get that gut feeling. *Autoimmunity Reviews*. 2015;**14**(11):1038-1047

