UDC 616.98-036:578.825.13:575.174.015.3

INFUENCE OF GENE POLIMORPHISM ON THE COURSE OF EPSTEIN-BARR VIRUS INFECTION

Sorokina O.G.

Mechnikov Institute of microbiology and immunology, V.N. Karazin Kharkov National University

Introduction

Currently, infectious diseases occupy a dominant place in human pathology and, according to forecasts of experts of the World Health Organization, in the 21st century the role of infection in the structure of overall morbidity will be increasing [12]. The coming century is the century of opportunistic infections due to the influence of unfavorable environmental factors on the body and, above all, on the immune system [3, 4]. Among the many factors that directly affect the immune system, special attention should be paid to the viruses of the herpes family [5, 6, 7, 8, 9].

Epstein-Barr virus belongs to the family Herpesviridae subfamily Gammaherpesvirinae to the genus Lymphocriptovirus, and is a herpes simplex virus type 4 [10, 11, 12, 13, 14, 15, 16, 17].

The relevance of the Epstein-Barr virus infection (VEB) is due to a high degree of infection of the population around the world, as well as specific antibodies to this virus, detected in almost 95% of the adult population. [18, 19].

At the present stage of development of medical science, infectious mononucleosis (MI), caused by the Epstein-Barr virus (EBV), remains an important problem. This is due to the ubiquitous spread of the pathogen, its potential oncogeneity, lifelong persistence in the human body, and the lack of means of etiotropic therapy and prevention [1, 6, 10, 20].

At the end of the acute period of the disease, all herpes viruses without exception are not eliminated from the body [21]. This fact, first of all, and later consequences of the transferred infection. Even in a fully functioning immune system, it is possible to reactivate herpesviruses throughout the life of the host, replication with the formation of postpartum depression and further association with malignancy [22, 23, 24, 25, 26].

Previously, MI was considered a self-limiting disease, so as a clinically pathogenetic manifestation of this infection is a benign lymphoproliferative process [27, 28, 29, 30, 31, 32, 33].

The assumption of the good quality of MI caused by VEB, which is recognized by the overwhelming majority of researchers, is based on the fact that the acute period of the disease in most cases ends clinically safely [34, 35, 36, 37, 38, 39]. Coping of the main clinical symptoms of the disease, usually occurs by the 10-14 day of the disease. After the end of inpatient treatment, the manifestations of the defeat of the lymphoid apparatus are significantly reduced in most children. However, according to a number of researchers, about two-thirds of patients at the time of discharge from hospital have residual manifestations of the disease, which are most often related to changes in the lymphatic system and liver [20, 41, 42, 43, 44]. Moderate increase in the lymph nodes of the cervical group is observed in almost all convalescents of myocardial infarction, and about 20% of patients, according to VV. Fomin, et his coauthors [45] by the end of the year have an objective increase in the liver, not associated with any other gastroenterological pathology. A number of authors define liver damage in infarction as a specific viral hepatitis, suggesting the need for prolonged clinical examination to determine the significance of this disease in the formation of chronic hepatitis [46, 47, 48, 49, 50].

Immunologists from different countries have accumulated sufficient material on the study of immunopathology in infarction, which made it necessary to reconsider the attitude towards this disease as to an absolutely benign one and to prove the possibility of its protracted and chronic course [51, 52, 53, 54, 55].

At the present stage, considering the presence of a large number of patients who have a long period of one or another complaint, it becomes necessary to study this issue. The study of the issue, the presence of what features of the individual determines the difference in the scenario of the course of their disease, is of particular interest. In this paper, we have decided to study why, in one group of patients, there is a slight course, a tendency to self-healing, and all complaints quickly disappear, while the other group has a tendency to develop a protracted course and a chronic process. We have made the assumption that the possible course of the disease correlates with the difference in genetic factors.

As a result of the conducted scientific researches, the important role of single nucleotide polymorphisms (SNPs) that influence the formation of the immune response, the intensity of nonspecific immune responses and form a predisposition to various diseases has already been revealed. These data allow a new assessment of the role of genetic polymorphism as host and pathogen [56].

There are works in which the influence of the genetic factors of the human body on the favorable course of a particular viral disease was studied.

In the present work, we have decided to study the effect of gene polymorphism in patients with Epstein-Barr virus infection on flow auspiciousness and prognosis.

To focus on the study of the level of cytokines (in particular interleukin-28) was of particular interest.

IL28A, IL-28B and IL-29, also called interferon-lambda (INF-λ) 2,3 and 1, respectively, belong to the family of class 2 cytokines and are a newly discovered group of antiviral cytokines. INF-λ and induces antiviral, antiproliferative, antitumor and immune effects.

The proteins of the INF-λ family have less antiviral activity compared to INF-α in vitro [57]. There are studies showing that INF-λ3 inhibits some viruses, depending on the dose and time of exposure, increases the expression of interferon-stimulated genes (ISGs, interferon stimulated genes), and increases the antiviral activity of INF-α [58]. The IL-28B gene is localized in the chromosome 19q13. Next to it, polymorphic loci were found (rs12979860, rs8099917).

The IL28B gene encodes an interferon-lambda-3 protein, which is a class II cytokine receptor ligand. IL28B triggers a JAK (signal transducer and activator of

DOI: 10.5281/zenodo.803868

transcription) signaling cascade that transmits information from extracellular polypeptide signals to the promoters of target genes, blocking the synthesis of viral proteins.

In world practice it is accepted that the dominant allele pair is called "wild" genotype, and the minor one is called "mutant" genotype. In this paper, we will adhere to the terminology - dominant and minor.

Single nucleotide polymorphism (SNP, from English Single nucleotide polymorphism, SNP,) is a DNA sequence of one nucleotide in the genome of representatives of one species or between homologous regions of homologous chromosomes.

The DNA region in the regulatory region of the IL28B gene, in which the cytosine (C) nucleotide is replaced by thymine (T), is designated as the genetic marker rs12979860 (designation of the NCBI arrester).

There are the following possible genotypes: C/C, C/T and T/T.

The region of DNA in the regulatory region of the IL28B gene, in which the thymine (T) nucleotide is replaced with guanine (G), is designated as the genetic marker rs8099917 (designation of the NCBI database arresters).

There are the following possible genotypes: T/T, T/G and G/G.

There are works in which it is demonstrated that interferon-λ proteins are important for the elimination of some viruses. In this paper, we have decided to study the probability and importance of their influence on the course and prognosis of the EBV infection.

A full-genomic association study (GWAS), published in 2009, revealed a clear link between genetic variations in the region of the IL-28B gene and the development of a persistent form of infection and spontaneous elimination of of some viruses [59]. The results showed that the polymorphism rs12979860 C > T in 19 chromosomes is associated with a stable virologic response (SVR). Studies by Y.Tanaka that were conducted among Japanese patients, V.Suppiah and A. Rauch among Europeans revealed another polymorphism (rs8099917 T > G) also localized near the IL28B gene, however these studies differ from GWAS by a smaller scale [59, 60, 61]. Tanaka, Suppiah and Rauch revealed a strong correlation between the SVR and the TT genotype rs8099917. It is possible that this may be due to the influence of polymorphic changes on the expression level of IL-28B. But the results of studies on the effect of these polymorphisms on the expression of IL-28B are contradictory.

According to the literature data, these two point nucleotide replacements of the IL-28B gene serve as markers for the spontaneous elimination of the virus and the effectiveness of treatment. However, their influence on pathogenesis, course and prognosis in patients of East Slavic origin has not been studied in practice, and the role of IL-28B on the course and prognosis of patients with VEB infection has not been studied [51, 52, 53, 54, 55, 59, 61].

The aim of this work was to study the polymorphism of genes in patients with VEB infection and to identify its effect on flow advantage and prognosis.

Material and methods

We have examined 96 patients with chronic VEB infection, the main clinical manifestations of which were various immunopathological and immunodeficiency states - I clinical group (Table 1), as well as 10 patients who had undergone a history of VEB without any complaints at the moment - II clinical Group. The age of the patients was from 20 to 65 years (mean age 35 years ± 10.7 years). Women were 63.5% (n = 61), men - 36.5% (n = 35) (male-male ratio: 1.2: 1.0), who were hospitalized in the regional clinical hospital in Kharkiv and were observed outpatient in polyclinics in Kharkov in 2014 - 2017.

The comparison group consisted of 10 clinically healthy people who had no record of infectious mononucleosis (III clinical group).

Table 1. Clinical observation groups

Observation groups	Amount of patients
Patients with different manifestations of EBV infection:	**96**
- *prolonged subfebrile condition*	*28*
- *nonspecific lymphadenopathy*	*26*
- *chronic tonsillitis*	*19*
- *chronic Fatigue Syndrome*	*14*
- *reactive arthritis*	*9*
Patients who are in anamnesis of VEB without any complaints at the moment	**10**
Control group	**10**
Total	116

The analysis was taken and their technical performance was carried out in the clinical and diagnostic laboratory of the Regional Clinical Infectious Disease Hospital, part of the analyses were performed in the laboratory of Virola. In the process of confirming the diagnosis, the patients underwent a general blood test, a complex of molecular genetic and serological studies.

Polymorphism of the genes was determined using the RFLP method (polymorphism of the length of restriction fragments) and the real-time PCR method using the Corbett Research Rotor-Gene-3000 and the DNA-detecting DT-96 amplifier.

To detect the polymorphisms under study, amplification of certain sections of the corresponding genes was carried out. To determine the allelic variation of the IL28B gene, a commercial DNA-technology test system was used. SNP 39743165T> G (rs8099917) and SNP 39738787C> T (rs 2979860) of the IL-28B gene were used to detect point mutations using polymerase chain reaction and polymorphism of restriction fragment lengths. As a material for the study, DNA obtained from leukocytes was used with commercial reagents to extract DNA from the clinical material "Cytolysin" by AmpliSens (Russia).

Detection of polymorphism of the gene IL-28B rs12979860 was carried out by real-time PCR on the detecting DT-96 amplifier of the DNA technology company. After denaturation (80 ° C, 2 min, 94 ° C, 5 min), amplification was carried out from 51 cycles, each

DOI: 10.5281/zenodo.803868

of which included denaturation (94 ° C, 30 s), primer annealing and elongation (67 ° C, 10 s) - 5 cycles; Denaturation (94 ° C, 5 sec), primer annealing and elongation (67 ° C, 5 s) - 45 cycles; One cycle at 25 ° C, 30 seconds. Automatic detection of amplification results was performed by the DT-96 instrument.

PCR was performed in a volume of 35 μl in a solution of the following composition: 20 μl primer solution, 10 μl Taq polymerase and buffer mixture, and 5 μl DNA.

The exponential growth in the amount of product in the FAM channel, and its absence in the HEX channel, is detected as the genotype CC; the growth in both channels is detected, like CT and only in the HEX channel - as TT. The exponential growth in the amount of product in the FAM channel, and its absence in the HEX channel, is detected as the genotype of the TT; the growth in both channels is detected, as TG and only in the HEX channel - as GG.

Statistical analysis comprised significant testing of the difference between means using a two tailed Student's t-test at the level 0.05.

Results and discussion

There were statistically significant differences in the allelic variations of the IL-28B gene in the study groups. Table 2 shows the results of the frequency of detection of individual allelic pairs in polymorphic loci of cytokine genes.

As can be seen from the data of the table, CC and CT variants prevailed in the locus rs12979860 for the IL-28B, TT and TG gene at the locus rs8099917 of the same gene.

Table 2. The frequency of detection of individual allelic pairs in polymorphic loci of cytokine genes.

Name of the gene and locus	Genotype	%
IL-28B: locus rs12979860	CC	46,62
	CT	41,32
	TT	12,06
IL-28B: locus rs8099917	TT	58,62
	TG	37,20
	GG	4,18

The following trend was also noted. A group of patients with a record of VEB who do not currently have any complaints, and also in the comparison group for the IL-28B gene, found the CC genotype at the locus rs12979860, and the TT genotype at the locus rs8099917. This suggests that in patients with chronic VEB infection, when the genotype of the CCV genotype in the locus rs12979860 and the TT genotype at the locus rs8099917 are detected in the IL-28B gene, a more favorable course and greater adherence to therapy will be required, and we will be able to observe in such patients an earlier and more stable virological response. We have also analyzed the combinations of different allelic variations in patients of different clinical groups under observation.

In the analysis of single nucleotide substitutions in the regulatory regions rs8099917 and rs12979860 of the gene IL28B, statistically significant evidence was obtained of a non-random combination of allele pairs CC and TT in individuals who had no complaints, but who had a record of VEB infection in the control group (Table 3).

Table 3. Combinations of CC and TT alleles in individuals in different clinical groups

IL-28B rs12979860	IL-28B rs8099917	I group	II group	III group	Significance level, p
		Patients with chronic VEB infection	VEB in the anamnesis in the absence of complaints at the moment	Control group (persons with no anamnesis EBV infection)	
CC	TT	**39,3**	**54,02**	**63,35**	**0,001**
	TG	2,1	1,76	1,76	p>0,05
	GG	0	0	0	-
CT	TT	24,60	16,6	12,3	p>0,05
	TG	22,74	16,2	11,9	p>0,05
	GG	0	0	0	-
TT	TT	1,03	1,73	1,27	p>0,05
	TG	6,12	6,56	6,56	p>0,05
	GG	4,11	3,13	2,86	p>0,05

Statistically significant evidence of a non-random combination of alleles CC and TT in individuals with a more favorable course of EBV infection was also obtained, and the number of episodes of exacerbation during the year is significantly less (Table 4).

Table 4. Different combinations of alleles among people with different variants of the Epstein Barr virus infection

IL-28B rs12979860	IL-28B rs8099917	I clinical group - patients with chronic VEB infection			Significance level, p
		The quantity of episodes of exacerbations during the year more than 5 times	The quantity of episodes of exacerbations during the year more than 5 times 4-5 times	The qantity of episodes of exacerbations during the year 1-2 times	

DOI: 10.5281/zenodo.803868

CC	TT	**25,25**	**42,50**	**50,15**	**0,001**
	TG	1,3	2,1	2,90	p>0,05
	GG	0	0	0	-
CT	TT	16,45	31,14	26,21	p>0,05
	TG	24,32	22,30	21,60	p>0,05
	GG	0	0	0	-
TT	TT	1,13	1,01	0,95	p>0,05
	TG	6,02	6,15	6,19	p>0,05
	GG	4,18	4,14	4,01	p>0,05

Conclusion

The data suggest that the IL-28B genotype is a significant factor influencing the favorable course of the VEB infection, the frequency and severity of episodes of exacerbation throughout the year, and even the probability of transition or non-transition of the disease to a chronic form, and is an important factor in the prognosis. A more favorable course of EBV infection was noted in patients with CC genotype at the locus rs12979860 and TT genotype at the locus rs8099917 compared with the genotypes of CT and TT in the locus rs12979860 and the genotypes GT and GG at the locus rs8099917. Thus, the study of the genotype of IL-28B is an urgent issue and requires further study.

References

1. Uchaikin V.F. Guide to infectious diseases in children / V.F. Uchaikin. - M.: GEOTAR Medicine, 1999. - 824 p.
2. Khmilevskaya S.A. Clinical and laboratory features of CMV-infectious mononucleosis / S.A. Khmilevskaya, I.A.Zaitseva, E. V. Mikhailova // Actual questions of the infectious pathology of ivacinoprophylaxis: mater. VI Congress. Children's infectious diseases in Russia. - M.,
3. Significance of markers of herpetic viruses for the evaluation of the health status of children / N. Yu. Egorova, FS Kharlamova, VF Uchaikin, etc. // Infant Infections. - 2008. - No. 2. - P. 16-21.
4. Keltsev, VA Functional state and interrelation of the immune system in the endocrine system in patients with Epstein-Barr virus mononucleosis / V.A. Keltsev, L.I.Grebenkina, E.V. Petrova // Children's infections. - 2005. - No. 1.
5. Isakov V.A. Herpesviral human infections: A guide for physicians / V. A. Isakov, E. I. Arkhipova, D. V. Isakov. - St. Petersburg. : SpetsLit, 2006. - 302 p.
6. Importance of markers of herpetic viruses for assessing the health of children / N. Yu. Egorova, F.S. Kharlamova, V.F. Uchaikin, etc. // Infant Infections. - 2008. - No. 2. - P. 16-21.
7. Keltsev V.A. Functional state and interrelation of the immune and endocrine systems in patients with Epstein-Barr virus mononucleosis. Keltsev, L.I.Grebenkina, E.V.Petrova // Children's infections. - 2005. - No. 1.- C. 29-32.
8. Clinical forms of chronic Epstein-Barr virus infection: diagnosis and treatment / I.K.Malashenkova, N.A.Didkovskiy, J.S. Sarsaniya and others // The attending physician. - 2003. - No. 9. - P. 23-27.
9. Fomin, V. V. Possible mechanisms of immediate type hypersensitivity in infectious mononucleosis in children / V.V. Fomin, E.E. Udilova // Ural. honey. Journal. - 2007. - No. 3. - P. 14-20.
10. Karazhas N.V. Epidemiological characteristics of cytomegalovirus infection and pneumocystis as opportunistic infections. Dis. Doct. Biol. Sciences. / - Moscow, 2002. - 181s.
11. Fundamentals of Immunology Yarilin A.A. M.: Medicine, 1999. - 608c.
12. Addi PA, Ahibor T., Amane S, Pappo M.A. Jaundice and infectious mononucleosis in Ghana. / / Afr. J. Med Sci. - 1978. - № 7. - from. 85-92.
13. Bagert B.A. Epstein-Barr virus with multiple sclerosis // Curr. Neurol. Neurosci. Rep.-2009.- No.9-p.405-410.
14. Chan C.W., Chiang A.K., Chan K.H., Lau A.S. Virus-associated infectious mononucleosis of Epstein-Barr in Chinese children. Pediatr Infect Dis J. - 2003. - No. 22. - p. 974-978.
15.Frade R., Barel M., et. And others. 140, C3d receptor of human B-lymphocytes, as well as the Epstein-Ban.-virus receptor // Proc. Native Acad. Sci. USA. - 1985. - Vol. XVI.-No.2. - p.419-427.
16. Tsega E., Mengesha B., Hansson B.G., Nordenfelt E., Lindberg J. Serological and demographic survey of Epstein-Barr virus infection in Ethiopia. // Trans R Soc Trop Med Hyg. - 1987. №81 .-p.677-680.
17. Herpes pathogenesis and laboratory diagnostics / Isakov V.A., Borisova V.V., Isakov D.V. St. Petersburg: 1999 - 190s.
18. Vozianova Zh.I. Infectious mononucleosis as the pulyetiological diseases / Z. I. Vozianova, A.I. Glay // Modern infections. - 2004. - No. 2. - P. 37-41.
19. Isakov V. A. Human herpesvirus infections: a guide for doctors. / Isakov V.A., Arkhipova E.I., Isakov D.V. - St. Petersburg, 2006. - 303 p.
20. Urazova O.I. Clinical-hematological and cytogenetic manifestations of infectious mononucleosis in children / O.I. Urazova, V.V. Novitsky, A.P. Pogogaeva // Epidemiology and infectious diseases. - 2004. -№3.-With. 34-40.
21. Epstein-Barr virus in hepatocellular carcinogenesis / W. Li, B.A. Wu, Y.M. Zeng et al. // World J. Gastroenterol. - 2004. - Vol. 10, № 23. - P. 3409 - 3413.
22. Detection of simultaneous Д-herpesvirus infections in clinical syndromes due to defined cytomegalovirus infection / R.R. Razonable, A. Rivero, R.A. Brown et al. // Clin. Transplant. - 2003. - Vol. 17, № 2. - P. 114 - 120.
23. EBV gH is essential for penetration of B cells but also plays a role in attachment of virus to epithelial cells / S. J.

Molesworth, C. M. Lake, C. M. Borza // J. Virol. - 2000. - Vol. 274, № 14. - P. 6324 - 6332.
24. Epstein-Barr virus (EBV) load and interleukin-10 in EBV-positive and EBV-negative post-transplant lymphoproliferative disorders / A. Airoldi, A. Alberti, E. Bonacina et al. // Br. J. Haematol. - 2003. - Vol. 122, № 6. - P. 927 - 933.
25. Epstein-Barr virus in hepatocellular carcinogenesis / W. Li, B.A. Wu, Y.M. Zeng et al. // World J. Gastroenterol. - 2004. - Vol. 10, № 23. - P. 3409 -3413.
26. Nielsen, L. A mucapture immunoassay for detection of human herpesvirus-6 (HHV-6) IgM antibodies in human serum / L. Nielsen, B.F. Velstergaard // J. Clin. Virol. - 2002. - Vol. 25. - P. 145 - 154.
27. Bokova, A.G. Clinical significance of immunological indices in infectious mononucleosis in children / A.G.Bokova, M.E. Domracheva // Children's infections. - 2006. - No. 3. - P. 18 - 22.
28. Bukina A.A. Clinico-etiological aspects and new approaches to the therapy of infectious mononucleosis in children: the author's abstract. Dis. cand. honey. Sciences / AA Bukin. - St. Petersburg, 2000. - 22 p.
29. Zhukova O.B. Viral Persistence: Immunological and Molecular-Genetic Aspects of Pathogenesis / OB Zhukova, NV Ryazantseva, B. V. Novitsky // Bull. Sib. Medicine. - 2003. - No. 4. - P. 113 - 120.
10. Infectious diseases in children / LF Bovtalo, AD Pleskachev, EM Simovanyan. - Rostov n / a: Phoenix, 2002. - 800 p.
31. Clinical and laboratory evaluation of the detection of markers of opportunistic infections in children with acute respiratory infections with airway obstruction / L.V.Feklisova, N.A. Savitskaya, N.V. Karazhas and others // Children's infections. - 2008. - No. 4. - P. 13 - 17.
32. Correlation between the development of thymomegaly in children and early infection with the Epstein-Barr virus and cytomegalovirus / M.M. Azova, O.B. Gigani, O.O.Gigani, etc. // Topical issues of infectious pathology in children: mother, congress . - M., 2004. - P. 23.
33. Cytomegalovirus mononucleosis / N. Yu. Egorova, L.N. Gusev, A.D. Chernousov, etc. // Children's infections. - 2003. - No. 4. - P. 24 - 26.
34. Anisimova, E. N. Infectious mononucleosis / E. N. Anisimova, N. B. Protopopova // First Territorial. - 2003.- № 18.- C. 35 -40.
35. Bokova, AG Clinical significance of immunological Indicators in infectious mononucleosis in children / AG Bokova, ME Domracheva // Infant Infections. - 2006. - No. 3. - P. 18 - 22.
36. Infectious mononucleosis associated with the herpesvirus type 6 / EV Novosad, OV Shamsheva, ND Lvov, etc. // Infant Infections. - 2008.-No.1-S. 36-38.
37. Infectious mononucleosis: clinic, pathogenesis, new in diagnosis and therapy / V.V. Ivanova, G.F. Zheleznikova, O.A. Aksenov and others // Infectious diseases. - 2004. - No. 4. - P. 5 - 12.
38. Clinical and laboratory characteristics, condition of the oropharynx and local immunity factors in Epstein-Barr patients with viral infectious mononucleosis / E.G.Belova. - M.: B. and., 2000. - 24 p.
39. Mücke, NA HHV-6 Associated infection in the structure of febrile illness in children and adolescents / N.A. Mücke, I. V. Zubkova // Vopr. Sovrem, pediatrics. - 2006. - No. 1. - P. 401.
40. Gulman L.A. Clinical and serological criteria for infectious mononucleosis in children / L.A. Gulman, L.M.Kurtasova, A.A. Andreeva // Children's infections. - 2004. - No. 3. - P. 27 - 30.
41. Immunological criteria for prescribing immunocorrecting drugs for infectious mononucleosis in children / G.F. Zheleznikova, V.V. Ivanova, A.S. Levina, etc. // Allergology and Immunology. - 2006. - No. 3. - P. 335 - 336.
42. Infectious diseases in children / L.F. Bovtalo, A.D.Pleskachev, E.M. Simovanyan. - Rostov n / a: Phoenix, 2002. - 800 p.
43. Krasnov E.I. Clinic and Diagnostics of Infectious Mononucleosis in Infants / E.I. Krasnova // Infant Infections. -2004.-No.1-C.6-9.
44. The Intersection of Epstein-Barr Virus with the Germinal Center / E. R.Jill, A. David // J. Virol. - 2009. - Vol. 83, №8. - P. 3968-3976.
45. Fomin V.V. About possible mechanisms of immediate type hypersensitivity in infectious mononucleosis in children / V.V. Fomin, E.E. Udilova // Ural. honey. Journal. - 2007. - No. 3. - P. 14 - 20.
46. Structural-metabolic status of peripheral blood mononuclear cells in infectious mononucleosis / O.I.Urazova, V.V. Novitsky, A.P. Pogogaeva, etc. // Bul. Experiment. Biology and medicine. - 2001.-№ 5. - With. 571-573.
47. Epstein-Barr Virus and HLA-DPB1-0301 in young adult Hodgkin's disease / F.E. Alexander, R.F. Jarret, R.A. Cartwright et al. // Cancer Epidemiol. Biomarkers &Prevention. - 2001. - Vol. 10. - P. 705 - 709.
48. Faucher, S. Cyno-EBV, a cynomolgus monkey EBV-like virus, and its latent membrane protein 1 oncogene / S. Faucher // Dissertation Abstracts International. - 2003. - Vol. 63, № 9. - P. 4039.
49. Goldani L.Z. Treatment of severe infectious mononucleosis with famciclovir / L.Z. Goldani // J. Infect. - 2002. - Vol. 44,№ 2. - P. 92 - 93.
50. Nielsen L. A mucapture immunoassay for detection of human herpesvirus-6 (HHV-6) IgM antibodies in human serum / L. Nielsen, B.F. Velstergaard // J. Clin. Virol. - 2002. - Vol. 25. - P. 145 - 154.
51. Immunological criteria for prescribing immunocorrecting drugs for infectious mononucleosis in children / G.F. Zheleznikova, V.V. Ivanova, A.S. Levina, etc. // Allergology and Immunology. - 2006. - No. 3. - C.
52. Kann, N.Yu. Value of persistent herpesvirus infection in the formation of secondary immunodeficiency in frequently ill children / N. Yu. Kann // Infant Infections. - 2008. - No. 2. - P. 64 - 66.
53. Problems of diagnosis and classification of secondary immunodeficiencies / V.S. Shirinsky, N.M. Starostina, Yu. A. Sennikova, O. A. Malysheva // Allergology and Immunology. - 2000. - No. 1. - P. 62 - 70.
54. Prolonged immunosuppression and possible chronic infection in children with infectious mononucleosis / V.V.Ivanova, O.V.Rodionova, G.F. Zheleznikova, etc. // Ros. Conduct, perinatology and pediatrics. - 2003.-№4. - FROM. 50-59.

DOI: 10.5281/zenodo.803868

55. Epstein-Barr virus latent membrane protein 1 (LMP1) activates the phosphatidylinositol 3-kinase / Akt pathway to promote cell survival and induce action filament remodeling / C.W. Dawson, G. Tramountanis, AG. Ehopoulos, L.S. Young // J. Biol. Chem. - 2003. - Vol. 278, № 6. - P. 3694 - 3704.
56. Lander E.S., et al. Initial sequencing and analysis of the human genome. Nature. 2001;№ 409(6822):860-921.
57. Sheppard P. and coauthors, IL-28, IL-29 and their class II cytokine receptor IL-28R. Nature Immunoly, 2003; № 4 (1). – P. 63–68.
58. Marcello T. et al., Interferons alpha and lambda inhibit hepatitis C virus replication with distinct signal transduction and gene regulation kinetics. Gastroenterology. 2006 Dec; № 131(6). – P. 87–98.
59. Tanaka Y. et al., Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nature Genetics. 2009; № 41. P.1105–1109.
60. Suppiah V. and coauthors. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nature Genetics. 2009; № 41. P. 1100–1104.
61. Rauch A. and coauthors. Genetic variation in IL28B is associated with Chronic Hepatitis C and treatment failure: a genome-wide association study. Gastroenterology. 2010. Apr.; № 138(4). P.1338-1345.

UDC 616.98-036:578.825.13:575.174.015.3

INFUENCE OF GENE POLIMORPHISM ON THE COURSE OF EPSTEIN-BARR VIRUS

Sorokina O.G.

Introduction. Currently, infectious diseases occupy a dominant place in human pathology. The relevance of the Epstein-Barr virus infection (VEB) is due to a high degree of infection of the population around the world, as well as specific antibodies to this virus, detected in almost 95% of the adult population. **Material and methods.** We have examined 96 patients with chronic VEB infection, the main clinical manifestations of which were various immunopathological and immunodeficiency states, as well as 10 patients who had undergone a history of VEB without any complaints at the moment. The comparison group consisted of 10 clinically healthy people who had no record of infectious mononucleosis. Polymorphism of the genes was determined using the RFLP method (polymorphism of the length of restriction fragments) and the real-time PCR method using the Corbett Research Rotor-Gene-3000 and the DNA-detecting DT-96 amplifier. To detect the polymorphisms under study, amplification of certain sections of the corresponding genes was carried out. To determine the allelic variation of the IL28B gene, a commercial DNA-technology test system was used. SNP 39743165T> G (rs8099917) and SNP 39738787C> T (rs 2979860) of the IL-28B gene were used to detect point mutations using polymerase chain reaction and polymorphism of restriction fragment lengths. As a material for the study, DNA obtained from leukocytes was used with commercial reagents to extract DNA from the clinical material "Cytolysin" by AmpliSens (Russia). Statistical processing of the results of the study was carried out in accordance with the recommendations for statistical processing of biomedical data. The statistical software package STATISTICA 10.0 was used. **Results and discussion.** A group of patients with a record of VEB who do not currently have any complaints, and also in the comparison group for the IL-28B gene, found the CC genotype at the locus rs12979860, and the TT genotype at the locus rs8099917. This suggests that in patients with chronic VEB infection, when the genotype of the CC genotype in the locus rs12979860 and the TT genotype at the locus rs8099917 are detected in the IL-28B gene, a more favorable course. In the analysis of single nucleotide substitutions in the regulatory regions rs8099917 and rs12979860 of the gene IL28B, statistically significant evidence was obtained of a non-random combination of allele pairs CC and TT in individuals with a more favorable course of EBV infection was also obtained, and the number of episodes of exacerbation during the year is significantly less. **Conclusion.** The data suggest that the IL-28B genotype is a significant factor influencing the favorable course of the VEB infection, the frequency and severity of episodes of exacerbation throughout the year, and even the probability of transition or non-transition of the disease to a chronic form, and is an important factor in the prognosis. A more favorable course of EBV infection was noted in patients with CC genotype at the locus rs12979860 and TT genotype at the locus rs8099917 compared with the genotypes of CT and TT in the locus rs12979860 and the genotypes GT and GG at the locus rs8099917. Thus, the study of the genotype of IL-28B is an urgent issue and requires further study. **Keywords:** infectious mononucleosis, Epstein-Barr virus infection, genotype, cytokine, interleukin-28, the polymorphism of genes.