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Увеиты и их ассоциация с антигенами гистосовместимости класса 1

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Цель — оценить диагностическое и прогностическое значение аллелей антигенов гистосовместимости (HLA) класса 1 в развитии передних увеитов. **Материал и методы.** Проведено типирование на антигены гистосовместимости HLA класса 1 (А и В-локусы) у 137 пациентов с передним увеитом, наблюдавшихся в ФГБНУ «НИИ глазных болезней» с 2009 по 2016 г. Средний возраст больных составил 29±12,4 года. После тщательного сбора анамнеза, офтальмологического и лабораторного обследований при подозрении на ассоциацию воспалительного заболевания глаз с системным заболеванием пациенты были проконсультированы в ФГБНУ НИИР им. В.А. Насоновой. Типирование HLA-антигенов класса 1 (А и В-локусы) осуществляли с помощью стандартного микролимфоцитотоксического теста с использованием специфических анти-HLA-сывороток ЗАО «Гисанс» (Санкт-Петербург). Статистическую обработку материала проводили с помощью программы Statistica 6,0 с применением методов описательной и непараметрической статистики (критерий Манна—Уитни). **Результаты.** Проведенное типирование на антигены гистосовместимости (HLA) класса 1 показало выраженную положительную ассоциативную связь увеита с антигеном HLA-B27 (p<0,00001). Выявлена также тенденция к снижению частот антигенов B7, B12 и B21 (p=0,1), однако различия в частотах этих антигенов в группе больных и в контроле не были статистически значимыми. Статистически значимых различий в частоте других HLA класса 1 у больных с увеитами в сравнении с показателями контрольной группы получено не было. **Заключение.** Исследование подтвердило ассоциацию некоторых антигенов гистосовместимости с определенными нозологическими заболеваниями, но статистически достоверной эта связь была только у заболеваний, ассоциированных с HLA-B27 антигеном.

Ключевые слова: *увеит, HLA-антигены, спондилоартриты, болезнь Бехчета, псориаз, псориатический артрит.*

Uveitis-associated HLA class 1 histocompatibility antigens

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Aim — to evaluate the diagnostic and prognostic significance of HLA class 1 histocompatibility antigens in the development of anterior uveitis. Material and methods. A total of 137 patients with anterior uveitis followed up at the Research Institute of Eye Diseases in 2009—2016 were tested for HLA antigens (A and B loci). The average patient's age was 29±12.4 years. All patients underwent a thorough medical interview with clinical and laboratory assessment. In case of suspected association with systemic disease, the patients were referred for consultation at the V.A. Nasonova Research Institute of Rheumatology. HLA typing was performed using a standard microlymphocytotoxicity test with specific anti-HLA sera (production of Gisans CC, Saint Petersburg). Statistical processing was performed with Statistica 6.0 software by applying methods of descriptive and nonparametric statistics (Mann—Whitney test). Results. The results of HLA class 1 typing indicated a significant positive association between uveitis and the HLA-B27 antigen (p<0.00001). Moreover, there was a trend toward decreased frequencies of B7, B12, and B21 antigens (p=0.1), however, the changes were not statistically significant as compared to the control group. Other HLA class 1 antigens also did not differ significantly in frequency between uveitis patients and the controls. Conclusion. The study has confirmed an association between certain histocompatibility antigens and systemic diseases. However, a statistically reliable relationship has been established only for the HLA-B27 antigen.

Keywords: *uveitis, HLA antigens, spondyloarthritis, Behcet's disease, psoriasis, psoriatic arthritis.*

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Social aspect of uveitis mainly affects the young working population because diseases of the vascular tract can cause significant sight decline or its complete loss. The etiology of uveitis is seldom determined. However, some forms of uveitis are linked to the presence of a certain leukocyte antigen (HLA) in the genotype of patients [1]. It is important when considering the diseases with unspecified etiology, chronically persistent conditions and immunological changes.

Studies conducted in the recent decades showed that genes encoding histocompatibility antigens are multifunctional, i.e. their clinical significance beside transplantology includes susceptibility to certain diseases. Biological significance of histocompatibility antigens pro-

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moted a new line of clinical research called "HLA and diseases" [2–4]. Certain HLA-antigens are associated with specific diseases indicating genetically induced predisposition – programmed risk of the onset of some forms of diseases [5–6]. Association of HLA with diseases has specific nature and is not related to potential damage of the genetic apparatus; the issue lies in the programmed risk factors manifesting in healthy population over time [7]. When trying to reveal the associations between histocompatibility antigens (HLA) and various diseases, the most conclusive are methods of population and family analyses. Population analysis usually involves blood typing of healthy and nosological groups followed by comparison of genes or antigens frequencies [8]. Family analysis enables unveiling or dismissal of the genetic predisposition for certain diseases, as well as revealing the associations of HLA genes with each other or with other genes. Linking HLA with a disease is based on both genetic determinacy and genetic association (L. Lamm, 1980) [9]. However, most often the connection between HLA and a disease takes the form of associations manifesting with varying strength. In such cases, only predisposition for pathology can be considered. A large group of diseases has been discovered to have certain associations with specific antigens and haplotypes (sets of antigens). According to A. Sveitjaard et al. (1979) [5], association of HLA antigens with diseases is purely quantitative and does not mean absolute imminence of the disease manifestation for people with risk antigens, while also does not exclude people without those antigens from having the disease [10]. This motivates studying of the mechanisms of uveitis onset as it can substantially contribute to the understanding of pathogenesis, clinical prognosis, effectiveness of early diagnostics, treatment, prevention of relapses and complications.

The purpose of this study is to evaluate the diagnostic and prognostic significance of HLA class 1 histocompatibility antigens in the development of uveitis.

Material and methods

The study group included 137 patients (79 males and 58 females) with anterior uveitis (AU) aged 29±12.4 years in average. All the patients were followed up at Research Institute of Eye Diseases during 2009–2016 years. The patients were tested for HLA antigens (A and B loci). Among the patients of the study group were 12 patients with inflammatory process transferred to the posterior parts of the eye: 3 had chorioretinitis, 2 – vasculitis, 4 – optic nerve (ON) neuropathy, 3 – panuveitis. All the patients underwent a thorough medical interview followed by standard clinical assessment methods such as visometry, biomicroscopy, ophthalmoscopy, tonometry, ultrasound examination (B-mode) of the eyes. When necessary, the patients also underwent optical coherent tomography (OCT) of the retina and ON, fundus fluorescein angiography (FFA), computer perimetry and electrophysiological (EP) study.

Laboratory assessment of the patients included clinical analysis of blood and urine, blood examination for viral and anti-bacterial antibodies that can be etiological agents of the uveitis development. When patients were suspected to have infections, they were referred for consultation to specialized institutions – Research Institute of Tuberculosis, Moscow Scientific and Practical Toxoplasmosis Centre, Faculty of Parasitology at Sechenov First Moscow State Medical University. To exclude inflammatory diseases of intestinal and urinogenital tracts the patients were examined by a proctologist, an urologist and a gynecologist. When association of the inflammatory disease of the eye with systemic disease was suspected, the patients were examined at Nasonova Research Institute of Rheumatology.

All the patients underwent typing for HLA class 1 antisera in the genetic laboratory at Nasonova Research Institute of Rheumatology. Typing for class 1 HLA antigens (A and B loci) was performed using standard microlymphocytotoxic test with specific anti-HLA sera manufactured by Gisans CC, Saint Petersburg. Study control group consisted of 150 healthy test-donors that had underwent typing at Immunology Institute of Federal Bio-Medical Agency (Moscow). Statistical processing of the data was performed with Statistica 6.0 software by applying methods of descriptive and nonparametric statistics (Mann-Whitney test).

Results

The study of HLA class 1 showed that 71 patients (51.8%) with uveitis had increased frequency of HLA-B27 – reliably more than in the control group that had 11 patients (7.3%) with such increase ($p<0.00001$). Additionally, a tendency towards a decrease in the frequency of some antigens was seen in comparison to the control group: B7 – 19 (13.9%) and 32 (21.3%) cases respectively (odds ratio (OR)=0.6 [0.3–1.1], $p=0.1$); B12 – 13 (9.5%) and 24 (16.0%) respectively (OR=0.6 [0.3–1.1], $p=0.1$); B21 – 2 (0.7%) and 8 (5.3%) respectively (OR=0.2 [0.05–1.2], $p=0.1$). Those differences, however, were statistically unreliable. Distribution of loci A and B HLA-antigens among the study patients and in the control group is shown in the **Table 1**.

Among HLA-B27-positive patients with anterior uveitis (AU), 47 (66.2%) were diagnosed with various forms of spondylarthritis (SpA) – spinal and joint infections with frequent uveitis comorbidity: 32 had ankylosing spondylitis (AS), 5 – psoriatic arthritis (PsA) in the setting of cutaneous psoriasis (overlapping), 2 – reactive arthritis (ReA), 5 – undifferentiated (USpA) and 3 – overlap of Behcet's disease (BD) and SpA (**Table 2**). Remaining 24 patients (33.6%) were diagnosed with B27-associated AU. Traditionally, uveitis in the setting of SpA is described as often relapsing acute one-sided process

Table 1. **Distribution of HLA-antigens in AU patients and healthy control group**

HLA antigens	Uveitis, *n*=137		Control, *n*=150		OR [95% CI]	*p*
	Frequency					
	antigen, *n* (%)	gene	antigen, *n* (%)	gene		
			Locus A			
A1	29 (21,2%)	0,0408	35 (23,4%)	0,1248		>0,05
A2	74 (54,0%)	0,1175	74 (49,3%)	0,2880		>0,05
A3	30 (21,9%)	0,0427	36 (24,0%)	0,1282		>0,05
A9	39 (28,5%)	0,0565	33 (22,0%)	0,1168		>0,05
A10	22 (16,1%)	0,0310	27 (18,0%)	0,0945		>0,05
A11	14 (10,2%)	0,0372	17 (11,3%)	0,0582		>0,05
A19	36 (26,3%)	0,0518	34 (22,7%)	0,1208		>0,05
A28	6 (4,4%)	0.0083	12 (8,0%)	0,0408		>0,05
			Locus B			
B5	17 (12,5%)	0,0237	23 (15,3%)	0,0797		>0,05
B7	19 (13,9%)	0,0266	32 (21,3%)	0,1127	0,6 [0,3—1,1]	0,1
B8	15 (11,0%)	0,0237	20 (13,3%)	0,0689		>0,05
B12	13 (9,5%)	0,0178	24 (16,0%)	0,0835	0,6 [0,3—1,1]	0,1
B13	17 (12,5%)	0,0237	15 (10,0%)	0,0513		>0,05
B14	6 (4,4%)	0,0266	10 (6,7%)	0,0341		>0,05
B15	10 (7,3%)	0,0138	18 (12,0%)	0,0619		>0,05
B16	9 (6,6%)	0,0124	13 (8,7%)	0,0445		>0,05
B17	10 (7,3%)	0,0138	12 (8,0%)	0,0408		>0,05
B18	12 (8,8%)	0,0167	15 (10,0%)	0,0513		>0,05
B21	2 (0,7%)	0,0014	8 (5,3%)	0,0258	0,2 [0,05—1,2]	0,1
B22	4 (2,9%)	0,0054	7 (4,7%)	0,0238		>0,05
B27	71 (51,8%)	0,1116	11 (7,3%)	0,0372	13,4 [6,8—27,3]	<0,00001
B35	28 (20,4%)	0,0394	30 (20,0%)	0,1056		>0,05
B37	2 (1,6%)	0,0033	4 (2,7%)	0,0136		>0,05
B40	16 (11,7%)	0,0222	18 (12,0%)	0,0619		>0,05
B41	9 (6,6%)	0,0124	3 (2,0%)	0,0101		>0,05
B47	—		1 (0,7%)	—		>0,05

Таблица 2. **Частота развития заболеваний из группы СпА у пациентов с ПУ в зависимости от выявляемости HLA B27**

Detection of HLA B27	Uveitis etiology		Number of patients, *n* (%)	Association with HLA-antigens
HLA B27+ 71 (51,8%)	SpA	AC	32	B 27
		PsA + cutaneous Ps overlapping	5	B 27, 13
		ReA	2	B 27
		UspA	5	B 27
		BD + SpA overlapping	3	B 27, 5(51)
Итого			47 (66,2%)	
HLA B27– 66 (48,2%)	SpA	PsA	4	B 13, B17(57)
		BD	2	B 5(51)
Subtotal:			6 (9,1%)	

mainly affecting anterior parts of the eye. Bilateral uveitis is rare, while sequential is typical for SpA [11—16]. Isolated affection of posterior parts of the eye (choroid, retina) is uncharacteristic for SpA; in certain cases, however, the inflammation debuting as iridocyclitis can spread to the posterior parts of the eye evolving into panuveitis.

Behcet's disease (BD) is a systemic vasculitis featuring varying ulcers in the mouth cavity and on the genitals, uveitis, and pathology of nervous system, intestinal tract and skin. Uveitis is one of the most severe manifestations of BD, in which case it can have any localization – anterior, posterior or panuveitis. Anterior uveitis (AU) develops as acute bilateral nongranulomatous affection lasting up to 2–3 months with high amount of inflammatory cells in the anterior segment of the eye, iris edema, and frequent hypopyon, which is an important distinguishing feature of uveitis in patients with BD. The uveitis is characterized by acute recurrent progression. Affection of the

posterior parts of the eye significantly worsens the disease prognosis in patients with BD. Eye affection is revealed in about 59% of patients with BD; it manifests 2.5 times more often in male patients than in female patients [17].

The genetic marker of BD is a histocompatibility antigen HLA-B5(51) with detection rate of up to 75% in BD patients, as opposed to 30% in healthy people. It is reliably more frequently seen in patients with eye pathology [18, 21].

The original SpA classification suggested by the concept's originators J. Molli and T. Wright in 1974 [20] is known to include BD based on the common features attributable to both BD and SpA: conjunctival ulceration, nodal fever, uveitis, arthritis. Back pain, as well as radiological signs of spondylitis and sacroiliitis are observed in a portion of BD patients (1.6–52%). According to Alekberova Z.S. (2013) [17], about 6% of BD patients with eye affection had combination of HLA-B5(51) and B27. The combination of antigens HLA-B27 and B5(51) is the foundation for overlapping clinical symptomatology of patients with signs of BD and SpA. In this study, among 17 (12.4%) patients with uveitis possessing B5(51)-antigen, five (29.4%) were diagnosed with BD, and three of them had the combination of HLA-B5(51) and B27 **(see Table 2)**.

HLA-B27-antigen was not detected in 66 patients (48.2%) with AU, who also were diagnosed with SpA significantly less frequently – only 6 (9.1%) AU patients were affected by it: 2 – with BD (HLA-B5(51), 4 – with PsA (HLA-B13, 17 (57)) **(see Table 2)**, which are known to be associated with psoriasis (Ps) and PsA [22–24]. B13 antigens were also detected in 3 patients with AU in the setting of cutaneous psoriasis **(see Table 2)**.

PsA is one of the basic inflammatory diseases of the joints and the spinal cord, and it is associated with Ps [22, 23]. Despite the current uncertainty about PsA causes, the role of genetic factors in the disease's development is apparent [23–25]. Major histocompatibility complex (MHC) is known make up 30% of the PsA genetic composition. According to various researchers, the frequency of eye affection in Ps patients is about 31%, with uveitis observed in 18% of patients with psoriatic affection of the joints and the spinal cord [22, 23]. Clinical implications of uveitis in half of the patients with Ps and PsA feature bilateral affection of the posterior segment of the eye, while for the other half the implications are similar to those in HLA-B27-associated uveitis and feature nongranulomatous AU. Uveitis and SpA develop concurrently in the majority of PsA patients, and eye inflammation onset coincides in time with the onset of the joint syndrome, although in certain cases uveitis precedes arthritis by 1–4 years [24].

Among the significant part (60 (90.9%)) of HLA-B27-antigen negative patients, 29 (48.3%) were diagnosed with uveitis of infectious etiology (viral, bacterial and parasitic), 5 (8.3%) – with other systemic diseases: one patient had sarcoidosis, one – tuberculosis, one – Hashimoto's thyroiditis, one – Fuchs endothelial dystrophy, and one – Vogt-Koyanagi-Harada syndrome; in 26 (43.3%) of patients the uveitis etiology remained unclear.

Conclusion

Marked positive association of HLA-B27 antigen with AU was established (OR=13.4 [6.8–27.3], $p<0.000001$). A tendency towards a decrease in the frequency of antigens HLA-B7, B12 and B21 was also revealed; however, the differences in frequencies between the study patients and the control group were not statistically reliable. B27-associated uveitis is one of the most common forms of uveitis, which is consistent with the literature data [10, 14–16] and with the results of this study. Detection of HLA-B27-antigen in AU patients requires searching for an SpA disease, detection of B13 and B17(57) – for psoriasis and PsA, and detection of B5(51) – searching for Behcet's disease. Association of B5(51) with BD and B13, 17(57) with PsA was not statistically confirmed in this study; however, it matched the results of other researchers [17, 18, 21–25]. In the absence of HLA-B27 in patients with uveitis, an SpA disease is less probable and the uveitis may be attributed to an infection (viral, bacterial, parasitic) or other systemic diseases.

Further research on the association between uveitis and MHC antigens may require larger study group.

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Study conception and design: I.R.
Collection of data: I.R., A.G., O.V.
Genetic research: I.G.
Statistical analysis: I.G., I.R.
Drafting of manuscript: I.R., A.G.
Critical revision: A.G., I.R.

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ЛИТЕРАТУРА/REFERENCES

1. Hou S, Kiilstra A, Yang P. Molecular Genetic Advances in Uveitis. *Prog Mol Biol Sci*. 2015;134:283-298. https://doi.org/10.1016 bs. pmbts 2015. 04.009
2. Blumental VN, Amos DB, Noreen H, Yunis EJ. Genetic mapping of the Ir locus in man: Linkage to second locus of HLA. *Science*. 1974;184:1301-1303.
3. Bodmer WF. Population studies and the measurement of natural selection, with special reference to the HLA system. *Isr J med Sci*. 1973;9(9-10): 1503-1518.
4. Хаитов Р.М., Алексеев Л.П. Физиологическая роль главного комплекса гистосовместимости человека. *Иммунология*. 2000;3:4-11. [Khaitov RM, Alekseev LP. Physiology role of main complex of human hystocompatibility. *Immunologia*. 2000;3:4-11. (In Russ.)].
5. Sveijgaard A, Ryder L.P, HLA markers and disease. Genetic Anal Common Diseases New York. *Prog Clin Biol. Res*.1979;32:523-543.
6. Nepom BS. The role of the major histocompatibility complex and disease Susceptibility. *Immunol, immunopathol*.1993;67:50-55.
7. Петров Р.В. Иммунология и иммуногенетика. М.: Медицина: 1976. [Petrov RV. Immunologia i immunogenetica. M.: Meditsina. 1976. (In Russ.)].
8. Певницкий Л.А. Статистическая оценка ассоциации HLA антигенов с заболеваниями. *Вестник АМН СССР*. 1998;7:48-51. [Pevnitsky LA. Statistical estimate of HLA antigens association with diseases. *Vestnik Academii medicinskich nauk SSSR*. 1998;7:48-51. (In Russ.)]
9. Lamm LV. HLA-DR matching and pool sise requirement. *Lancet*. 1980;2(8197):755.
10. Huhtinen M, Karma A. HLA-B27 typing in the categorization of uveitis in HLA-B27 population. *Br J Ophthalmol*. 2000;84:413-416.
11. Gouveia E, Elmann D. Ankylosing spondylitis and uveitis:Overview Bras. *Rheumatol*. 2012;52(5):742-756.
12. Fernandes-Melon J, Munos-Fernandes S, Hidalgo V, Bonilla-Hernan G, Schlincker A, Fonseca F, Vieities J, Martin-Mola T. Uveitis as the Initial clinical Manifestation in patients with spondyloarthropathies. *The Journal of Rheumatology*. 2004;31(3):524-527.
13. Nepom BS, Nepom GT. Immunogenetics of the rheumatic diseases. In Kelley WK, Harris E, Ruddy S, Sledge CB, eds. Textbook of Rheumatology, 4th ed. Philadelphia. W.B. Saunders; 1993:89-107.
14. Zagora SL, Mc Glusky PS. Ocular manifestation of seronegative Spondyloarthropathies. *Curr Opin Ophthalmol*. 2014;25(6):495-501. https://doi.org/10.1097icu.0000000000000000098
15. Brophy S, Pavy S, Lewis P, Bradbury L, Robertson D, Lovell C, CalinA. Inflammatory eye, skin and bowel disease in spondiloarthritis:genetic, phenotypic, and environmental factors. *Rheumatol*. 2001;28(12):2667-2673.
16. Годзенко А.А., Разумова И.Ю., Бочкова А.Г. Клиническая оценка увеита и ее значение в диагностике спондилоартритов. *Научно-практическая ревматология*. 2011;6:38-42. [Godzenko AA, Razumova IY, Bochkova AG. Clinical evaluation of uveitis and its role in spondiloarthritis diagnostic. *Nauchno-prakticheskaya revmatologia*. 2011;6:38-42. (In Russ.)]
17. Голоева Р.Г., Алекберова З.С., Гусева И.А., Крылов М.Ю. Болезнь Бехчета и ассоциации с антигеном HLA-B5. *Терапевтический архив*. 2010;5:45-50. [Goloeva RG, ALekberova ZS, Guseva IA, Krilov MY. Behcet's Diseases and its association with HLA-B5 antigene. *Ter. Arkhiv*. 2010;5:45-50. (In Russ.)].
18. Алекберова З.С. Болезнь Бехчета. *Научно-практическая ревматология*. 2013;51(1):52-58. [Alekberova ZS. Behcet's Disease. *Nauchno-prakticheskaya revmatologiya*. 2013;51(1):52-58. (In Russ.)]
19. Ohno S, Ohguchi M, Hirose S, Matsuda H, Wakisaka A, Aisawa M. Close association of HLA Bw 51 with Behcet's Disease. *Arch Ophtalmol*. 1982; 100:1455-1458.
20. Molli JM, Haslock I, Macrae IF, Wright TV. Association between ankylosing spondilitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet Syndrom. *Medicine (Baltimore)*. 1974;53:343-363. https://doi.org/10.1097/00005792-197409000-00002
21. Tugal-Tutkun J, Ona S, Altan-Yaycioglu R, Altunbas H.H, Urgahcioglu M. Uveitis in Behcet's disease:analysis of 880 patientis. *Am J Ophthalmol*. 2004;138:373-380.
22. Трошкина И.А., Бадокин В.В., Гусева И.А. Роль антигенов системы HLA класса 1 в развитии псориатического артрита и его клиническая презентация. *Научно-практическая ревматология*. 2012;53(4):34-39. [Troshkina IA, Badokin VV, Guseva IA. Role of the system HLA class 1 antigens in development of psoriatic arthritis and its clinical presentation]. *Nauchno-practicheskaya revmatologia*. 2012;53(4):34-39. (In Russ.)].
23. Федоров С.М. Псориаз: клинические и терапевтические аспекты. *Русский медицинский журнал*. 2001;9(11):447-450. [Fiodorov SM. Psoriasis:clinical and therapeutic aspects. *Rossyisky med. zurnal*. 2001; 9(11):447-450. (In Russ.)].
24. Lambert JR, Wright. Eye inflammation in psoriatic arthritis. *Ann Rheum Dis*. 1976;35 (4):354-356.
25. Довжанский С.И., Пинсон И.Я. Генетические и иммунные факторы в патогенезе псориаза. *Российский журнал кожных и венерических болезней*. 2006;1:14-18. [Dovzhansky SI, Pinson IYa. Genetic and immune factors in the pathogenesis of psoriasis. *Rossyisky zurnal kozhnich I venericheskich bolezney*. 2006;1:14-18. (In Russ.)].