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Original study article

Human leukocyte antigen class II (*DRB1* and *DQB1*) alleles frequencies in patients with bullous pemphigoid, Stevens–Johnson syndrome and toxic epidermal necrolysis in Russian population

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ABSTRACT

BACKGROUND: Bullous pemphigoid is known to be an autoimmune, life-threatening blistering skin disorder characterized by subepidermal blister formation. In bullous pemphigoid activation of B-cell immunity depends on the interaction between T-cell receptors and classic HLA II molecules. Similar interrelation has been revealed in a vast variety of studies on severe allergic reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. It was also suggested that Stevens-Johnson syndrome and toxic epidermal necrolysis might be associated both with HLA I and II classes.

AIM: To assess the prevalence of *HLA-DRB1* and *DQB1* alleles at a low and high-resolution levels in patients with bullous pemphigoid and Stevens-Johnson syndrome / toxic epidermal necrolysis.

MATERIALS AND METHODS: 29 Bullous pemphigoid, 14 Stevens-Johnson syndrome / toxic epidermal necrolysis patients and 92 health volunteers were included in the study. *HLA-DRB1* and *DQB1* alleles were assessed by polymerase chain reaction using specific primers.

RESULTS: At a low-resolution level, *HLA-DRB1*4* (p <0.02) and *DRB1*14* (p <0.0015) alleles were statistically significantly revealed in bullous pemphigoid patients compared to health controls. Additionally, at the high-resolution level the predisposing to bullous pemphigoid *HLA-DRB1*04:02* allele was also identified (p <0.01). At the low-resolution level of *HLA-DQB1* typing we displayed protective and predisposing to bullous pemphigoid alleles *HLA-DQB1*1* (p <0.01) and *HLA-DQB1*2* (p <0.039) respectively. At the low-resolution level of *HLA-DQB1* typing, the chances to obtain *DQB1*03:02* allele were 3.71 times higher compared to healthy volunteers (p <0.01). In patients with Stevens-Johnson syndrome / toxic epidermal necrolysis, *HLA-DRB1*4* allele was shown to be predisposing (p <0.03). For all other types of HLA alleles (*DRB1* and *DQB1*) at the high-resolution level no any statistically significant results have been observed in these patients.

CONCLUSION: We identified *HLA-DRB1*4*, *DRB1*14*, *DRB1*04:02* alleles predisposing to the development of bullous pemphigoid, with the *HLA-DQB1*1* allele being protective for the development of bullous pemphigoid and *HLA-DRB1*4* allele predisposing to the development of severe drug reactions of Stevens-Johnson syndrome / toxic epidermal necrolysis. No any protective alleles in Stevens-Johnson syndrome / toxic epidermal necrolysis patients were detected.

Keywords: bullous pemphigoid; Stevens–Johnson syndrome; toxic epidermal necrolysis; HLA-DRB1 and DQB1 alleles; HLA typing; Russian population.

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Оригинальное исследование

Оценка распространённости HLA аллелей II класса (*DRB1* и *DQB1*) у больных буллёзным пемфигоидом, синдромом Стивенса–Джонсона и токсическим эпидермальным некролизом в российской популяции

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АННОТАЦИЯ

Обоснование. Буллёзный пемфигоид представляет собой тяжёлое аутоиммунное заболевание кожи и характеризуется формированием субэпидермальных пузырей. Известно, что именно при буллёзном пемфигоиде активация В-клеточного иммунитета зависит от взаимодействия Т-клеточных рецепторов с классическими молекулами HLA II класса. Похожая взаимосвязь выявлена в различных исследованиях и при тяжёлых аллергических цитотоксических реакциях, таких как синдром Стивенса–Джонсона и токсический эпидермальный некролиз. Многие авторы продемонстрировали, что синдром Стивенса–Джонсона и токсический эпидермальный некролиз могут быть ассоциированы с HLA-аллелями I и II классов.

Цель исследования — оценить частоту распространённости *HLA-DRB1* и *DQB1* аллелей на уровнях низкого и высокого разрешения у больных буллёзным пемфигоидом и синдромом Стивенса–Джонсона / токсическим эпидермальным некролизом.

Материалы и методы. В исследовании приняли участие 29 больных буллёзным пемфигоидом, 14 с синдромом Стивенса–Джонсона / токсическим эпидермальным некролизом и 92 здоровых донора. HLA-типирование для *DRB1* и *DRQ1* проводилось с помощью полимеразной цепной реакции с применением специфических праймеров.

Результаты. На уровне низкого разрешения *HLA-DRB1*4* (p <0,02) и *DRB1*14* (p <0,005) аллели статистически значимо чаще выявлялись у больных буллёзным пемфигоидом по сравнению с группой контроля. На уровне высокого разрешения выявлен предрасполагающий к развитию буллёзного пемфигоида *DRB1*04:02* HLA аллель (p <0,01). На уровне низкого разрешения по *HLA-DQB1* обнаружены также протективные и предрасполагающие к развитию буллёзного пемфигоида аллели *HLA-DQB*1* (p <0,01) и *HLA-DQB1* (p <0,039) соответственно. На уровне низкого разрешения по *HLA-DQB1*1* шансы у больных буллёзным пемфигоидом получить *DQB1*03:02* аллель были в 3,71 раза выше по сравнению с группой здоровых доноров (p <0,01). У больных синдромом Стивенса–Джонсона / токсическим эпидермальным некролизом обнаружен предрасполагающий к заболеванию аллель *HLA-DRB*4* на уровне низкого разрешения (p <0,03). Для всех остальных видов HLA-типирования по *DRB1* и *DQB1* на уровне высокого разрешения у больных синдромом Стивенса–Джонсона / токсическим эпидермальным некролизом статистически значимых результатов не обнаружено.

Заключение. В нашем исследовании обнаружены предрасполагающие к развитию буллёзного пемфигоида аллели *HLA-DRB1*4*, *DRB1*14*, *DRB1*04:02*, при этом аллель *HLA-DQB1*1* был протективным к развитию буллёзного пемфигоида, *HLA-DRB1*4* — предрасполагающим к развитию тяжёлых лекарственных реакций синдрома Стивенса–Джонсона / токсического эпидермального некролиза. Протективных аллелей не обнаружено.

Ключевые слова: буллёзный пемфигоид; синдром Стивенса–Джонсона; токсический эпидермальный некролиз; *HLA-DRB1* и *DQB1* аллели; HLA-типирование; российская популяция.

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BACKGROUND

Bullous pemphigoid, an autoimmune, life-threatening blistering skin disease, primarily affects patients aged >60 years and is clinically characterized by the appearance of subepidermal blisters with a dense cap. In bullous pemphigoid, autoantibodies interact with the major bullous pemphigoid antigens located in the basement membrane region BP180 (non-collagenous domain 16 [NC16A] and BP230 [plakin family protein]) [1]. HLA alleles of classes I (HLA-A, HLA-B, and HLA-C), II (HLA-DR, HLA-DP, and HLA-DQ), and III (complement and cytokine genes) are important in the development of autoimmune diseases, such as multiple sclerosis, pemphigus, and diabetes types I and II. HLA class II alleles are directly responsible for the regulation of cellular immunity. Their main function involves binding and presenting peptide fragments on the cell surface to T- and natural killer cell receptors [1, 2].

HLA class II alleles are associated with antibody-mediated diseases. In bullous pemphigoid, the activation of antigen-specific B cells and the secretion of IgG antibodies depend on the interaction between T-cell receptors and classical HLA class II molecules [3, 4].

The relationship between HLA class II alleles and the development of bullous pemphigoid was identified in British, German, Chinese, Japanese, and Iranian populations [5–8]. For example, in the Chinese population, the authors revealed a higher incidence of the *HLA-DQB1*03:01* allele in patients with bullous pemphigoid compared with healthy donors. In addition, according to the study results, this allele increased T-cell tropism to various epitopes of BP180, particularly the BP-NC16A domain, and, therefore, played a key role in inducing the immune response to various antigenic domains in the basement membrane and forming the subepidermal bladder [1]. In the Chinese population, the *DQB1*05:01* and *DQB1*10:01* alleles are significantly more common [1].

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, drug-induced life-threatening diseases of an allergic nature and characterized by total detachment of the epidermis resulting from the activation of cytotoxic CD8+ T lymphocytes. TEN provokes Fas ligand, which interacts with Fas receptors on the surface of keratinocytes, thereby stimulating the activation of a cascade of caspase enzymes responsible for apoptosis and cell death [9]. These diseases are quite rare, with incidence ranging from 1.2 to 6 cases per 1 million people per year [10].

Antiepileptic drugs, allopurinol, and some antiviral drugs (abacavir) have demonstrated their relationship with HLA in many populations [9].

In general, HLA polymorphism depends on the so-called antigen-binding groove located in the lower part of *HLA-B*57:01*. For example, unchanged abacivir, which is used to treat HIV infection, binds to this groove and changes its shape and chemical composition, changing directly the repertoire of endogenous peptides capable of binding *HLA-B*57:01* [11, 12].

In 2004, W.H. Chung et al. [13] suggested that genetic factor plays one of the fundamental roles in SJS and TEN development, emphasizing the identified strong relationship between carbamazepine-induced SJS/TEN and the *HLA-B*15:02* allele. The same association was registered in Korean, Japanese, and European populations [14–16]. For example, in Taiwan, *HLA-B*15:02* screening reduced the incidence of carbamazepine-induced SJS and TEN [9]. Interestingly, other studies revealed an association between the *HLA-B*58:01* allele and allopurinol-induced SJS/TEN in Taiwanese, European, Japanese, Korean, and Thai populations [9, 14, 15, 17]. In the Russian population, the incidence of various HLA class II alleles in patients with bullous pemphigoid, SJS, and TEN has not been studied.

This study aimed to assess the prevalence of *HLA-DRB1* and *DQB1* alleles at low- and high-resolution levels in patients with bullous pemphigoid, SJS, and TEN.

MATERIALS AND METHODS

Study design

In this case–control study, the primary endpoint was the identification of differences in HLA class II *DRB1* and *DQB1* alleles in patients with bullous pemphigoid, patients with SJS/TEN, and healthy donors. This study had no intermediate endpoints.

Eligibility criteria

The *inclusion criteria* were as follows: histologically and immunohistochemically confirmed bullous pemphigoid and SJS/TEN and age of ⩾18 years.

The e*xclusion criterion* was as follows: patient's refusal to participate in the study.

Conditions

The study was conducted at the V.A. Rakhmanov Department of Skin and Venereal Diseases of the I.M. Sechenov First Moscow State Medical University of the Ministry of Health of Russia (Sechenov University); Academician P.V. Sergeev Department of Molecular Pharmacology and Radiobiology of the N.I. Pirogov Russian National Research Medical University of the Ministry of Health of Russia; and Blood Center of the I.M. Sechenov First Moscow State Medical University of the Ministry of Health of Russia, City Clinical Hospital No. 24 of the Moscow Healthcare Department.

Study duration

The study covered the period from 2016 to 2023.

Description of medical intervention

The bullous pemphigoid group received an initial dose of systemic glucocorticoids of 40–60 mg/day, followed by

its gradual decrease, as well as topical steroids. The SJS/TEN group received systemic glucocorticoids at a dose of 90–150 mg/day or pulse therapy with methylprednisolone at a dose of 1000 mg intravenously together with infusion therapy (potassium chloride + sodium chloride + magnesium chloride 400.0 mL intravenously), according to clinical recommendations. Venous blood tests were also performed to determine HLA alleles using HLA typing and real-time polymerase chain reaction (PCR).

Study outcomes

Main outcome of the study. A fatal outcome was recorded in a patient with carbamazepine-induced SJS. However, no severe complications were registered in the bullous pemphigoid group. The main outcome of the study was the identification of differences in the incidence of *DRB1* and *DQB1* HLA class II alleles in the bullous pemphigoid, SJS/TEN, and healthy donor groups using HLA typing in high and low resolutions.

Subgroup analysis

In the bullous pemphigoid group, 19 (65.5%) patients were female, and 10 (34.5%) patients were male. The SJS/TEN group included 10 women (71.4%) and 4 (28.6%) men (Fig. 1). SJS/TEN was caused by nonsteroidal inflammatory drugs in 36% of cases, amotrigine in 29%, and nonsteroidal aromatase inhibitors, allopurinol, dietary supplements, carbamazepine, and pantoprazole in 7% each (Fig. 2). The control group of healthy donors consisted of 40 (43.47%) men and 52 (56.53%) women (Fig. 1). For all diagnoses without exception, women predominate among patients, which may indicate the greater vulnerability of women in these types of dermatoses.

The average age of the bullous pemphigoid group was 60 (median 59) years. The greatest age range was noted in the SJS/TEN group. The youngest and oldest patients were 19 and 92 years old, respectively. On average, all patients were >40 years (Table 1).

Methods for recording outcomes

A blood sample was obtained from all patients for low- and high-resolution HLA typing of *DRB1* and *DQB1* alleles. The incidence of *DRB1* alleles was estimated at low (*HLA DRB1*4*, *DRB1*14*, *DRB1*13*, *DRB1*11*, *DRB1*1*, *DRB1*7*, *DRB1*15*, *DRB1*3*, *DRB1*16*; *HLA DQB1*5*, *HLA DQB1*3*, *HLA DQB1*6*, and *HLA DQB1*2*) and high (*DRB1*04:02*, *DRB1*14:05*, *DRB1*13:01*, *DRB1*11:04*, *DRB1*14:04*, *DRB1*15:01*, *DRB1*04:03*, *DRB1*07:01*, *DRB1*01:02*, *DRB1*13:02*, *DRB1*04:04*, *DRB1*14:01*, *DRB1*03:01*, *DRB1*16:01*, *DRB1*11:01*, *DRB1*01:01*; *DQB1*03:02*, *DQB1*05:03*, *DQB1*05:01*, *DQB1*03:01*, *DQB1*05:02*, *DQB1*02:01*, *DQB1*06:03*, *DQB1*06:04*, *DQB1*06:02*, and *DQB1*02:02*) resolutions. Alleles were registered using the Qiagen QIAamp DNAMini Kit (Germany). HLA typing for the *DRB1* and *DQB1* alleles was performed using 50 ng DNA extraction and PCR using specific primers (HISTOTYPE SSP Kits, BAG, Germany; AllSet+TM Gold SSP Typing Kits, Invitrogen Corp., Madison, Wi, USA). PCR products were separated by electrophoresis on a 2% agarose gel and stained with ethidium bromide. Images obtained were analyzed using HISTO MATCH software.

Ethical considerations

The study was approved by the ethics committee of Sechenov University (Protocol No. 03-22 of 02/03/2022).

Statistical analysis

Fisher's test was used to compare differences in the incidence of HLA alleles in sick and healthy donors. The strength of the association between HLA alleles and diagnoses was assessed using odds ratios and 95%

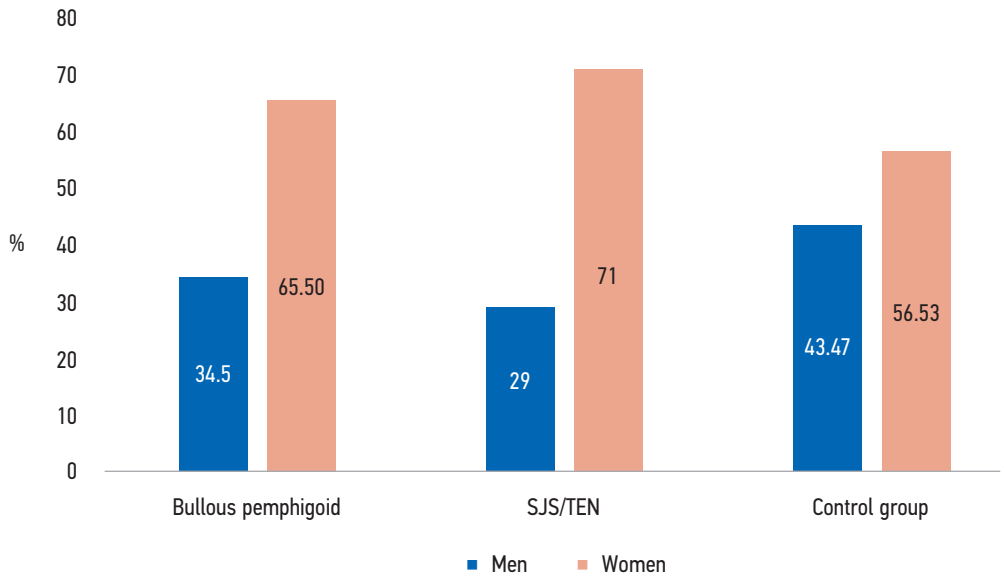

Fig. 1. Distribution of groups of sick and healthy donors by sex. ССД/ТЭН — Stevens–Johnson syndrome / toxic epidermal necrolysis.

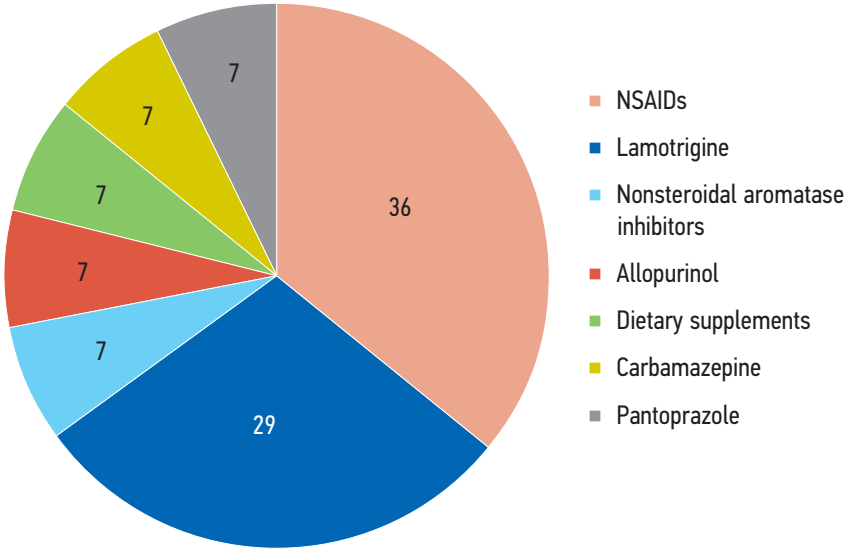

Fig. 2. Distribution of drugs that induced Stevens-Johnson syndrome/toxic epidermal necrolysis (%). НПВС — non-steroidal anti-inflammatory drugs; БАД — biologically active supplement.

Table 1. Distribution of patients by age

Diagnosis	Total	Min	Max	Mean	Median	MST
Bullous pemphigoid	29	23	86	~60	59	~19
SJS/TEN	14	19	92	~45	46,5	~20

Note. Ско — mean standard deviation. ССД/ТЭН — Stevens–Johnson syndrome / toxic epidermal necrolysis.

confidence intervals (chi-square test, χ^2). Quantitative indicators are described as mean and median values. *P* values were adjusted for multiple comparisons according to the Benjamini–Hochberg method.

RESULTS

Objects (participants) of the study

The study enrolled 43 patients with severe autoimmune skin diseases, including 29 patients with bullous pemphigoid, 14 patients with SJS/TEN, and 92 healthy donors.

Main results of the study

Low-resolution distribution of HLA DRB1 class II alleles in the bullous pemphigoid group. A significant result was obtained by calculating the values of *DRB1*14*. The odds of obtaining a *DRB1*14* value at the low-resolution level in the bullous pemphigoid group was 6.45 times higher than in the control group ($p = 0.0015$) (Table 2). A four-fold higher odds of obtaining *DRB1*4* values were registered in the bullous pemphigoid group compared with the control group ($p < 0.02$). Considering a significance level of 5%, the *p*-value, and confidence interval, calculated using the χ^2 test, the results were significant (Table 2). For the remaining *DRB1* values at the low-resolution level, considering a significance level of 5%, the results were not significant.

Low-resolution distribution of HLA DRB1 class II alleles in the SJS/TEN group. According to the χ^2 test, the *DRB1*14* allele was significantly more common at the low-resolution level in the SJS group than in the control group (Table 3). For the remaining *DRB1* values at the low-resolution level in the SJS group, given the significance level of 5%, confidence interval, and *p*-value calculated using the χ^2 test, the results were not significant (Table 3).

High-resolution distribution of HLA DRB1 class II alleles in the bullous pemphigoid group. At the high-resolution level, the *DRB*04:02* allele was significantly more common in the bullous pemphigoid group than in the control group ($p < 0.01$) (Table 4). For other types of *DRB1* HLA typing at the high-resolution level, no significant results were revealed (Table 4).

High-resolution distribution of HLA DRB1 class II alleles in the SJS/TEN group. For all types of *DRB1* HLA typing at the high-resolution level in this group, no significant result was obtained at a significance level of 5%, confidence interval, and *p*-value calculated using the χ^2 test (Table 5).

Low-resolution distribution of HLA DQB1 class II alleles in the bullous pemphigoid group. At the low-resolution level, the *DQB1*2* allele was significantly more common in this group than in the control group ($p < 0.039$), whereas *DQB1*1* was significantly more common in the control group (33.7%) than in the bullous pemphigoid group (6.9%) ($p < 0.01$) (Table 6). For all other HLA typing values, no significant results were obtained (Table 6).

Low-resolution distribution of HLA DQB1 class II alleles in the SJS/TEN group. For all values of *DQB1* HLA typing at the low-resolution level in this group, no significant results were

Table 2. Distribution of *DRB1* HLA typing at the low-resolution level for patients diagnosed with bullous pemphigoid and controls

DRB1	Study participants, *n* (%)		Statistical processing		
	Patients	Control group	Odds ratio (OR)	Confidence interval (CI)	*p*
14	**9 (31.03)**	**6 (6.52)**	**6.45**	**2.06–20.21**	**0.0015**
4	**8 (27.59)**	**8 (8.70)**	**4.00**	**1.34–11.90**	**0.02**
13	3 (10.34)	11 (11.96)	0.85	0.22–3.28	1
11	3 (10.34)	20 (21.74)	0.42	0.11–1.51	0.27
7	2 (6.90)	6 (6.52)	1.06	0.20–5.57	1
1	1 (3.45)	9 (9.78)	0.33	0.04–2.72	0.49
15	1 (3.45)	8 (8.70)	0.38	0.04–3.13	0.59
3	1 (3.45)	8 (8.70)	0.38	0.04–3.13	0.59
16	1 (3.45)	10 (10.87)	0.29	0.04–2.39	0.40

Note. A statistically significant result is highlighted with a bold font.

Table 3. Distribution of *DRB1* HLA typing at the low-resolution level for patients diagnosed with Stevens–Johnson syndrome/toxic epidermal necrolysis and controls

DRB1	Study participants, *n* (%)		Statistical processing		
	Patients	Control group	Odds ratio (OR)	Confidence interval (CI)	*p*
14	**4 (28.57)**	**6 (6.52)**	**5.73**	**1.38–23.83**	**0.03**
15	3 (21.43)	8 (8.70)	2.86	0.66–12.43	0.32
1	2 (14.29)	9 (9.78)	1.54	0.30–7.98	0.96
4	2 (14.29)	8 (8.70)	1.75	0.33–9.24	0.86
12	1 (7.14)	6 (6.52)	1.10	0.12–9.91	1
11	1 (7.14)	20 (21.74)	0.28	0.03–2.25	0.36
7	1 (7.14)	6 (6.52)	1.10	0.12–9.91	1

Note. A statistically significant result is highlighted with a bold font.

Table 4. Distribution of *DRB1* HLA typing at the high-resolution level for patients diagnosed with bullous pemphigoid and controls

DRB1	Study participants, *n* (%)		Statistical processing		
	Patients	Control group	Odds ratio (OR)	Confidence interval (CI)	*p*
*DRB1*04:02*	**7 (8.14)**	**5 (5.43)**	**5.54**	**1.6–19.11**	**0.01**
*DRB1*14:04*	6 (6.98)	0 (0)	-	-	-
*DRB1*14:05*	3 (3.49)	3 (3.26)	3.42	0.65–17.98	0.3
*DRB1*13:01*	3 (3.49)	11 (11.96)	0.85	0.22–3.28	1
*DRB1*07:01*	2 (2.32)	6 (6.52)	1.06	0.2–5.57	1
*DRB1*11:01*	2 (2.32)	5 (5.43)	1.29	0.24–7.02	1
*DRB1*01:01*	1 (1.16)	6 (6.52)	0.51	0.06–4.44	0.87
*DRB1*15:01*	1 (1.16)	8 (8.7)	0.38	0.04–3.13	0.59
*DRB1*04:03*	1 (1.16)	0 (0)	-	-	-
*DRB1*11:03*	1 (1.16)	0 (0)	-	-	-

Note. A statistically significant result is highlighted with a bold font.

Table 5. Distribution of *DRB1* HLA typing at the high-resolution level for patients diagnosed with Stevens–Johnson syndrome/toxic epidermal necrolysis and controls

DRB1	Study participants, *n* (%)		Statistical processing		
	Patients	Control group	Odds ratio (OR)	Confidence interval (CI)	*p*
*DRB1*14:04*	3 (21.43)	0 (0)	-	-	-
*DRB1*15:01*	3 (21.43)	8 (8.70)	2.86	0.66–12.43	0.32
*DRB1*04:02*	2 (14.29)	5 (5.43)	2.9	0.51–16.65	0.51
*DRB1*14:05*	1 (7.14)	3 (3.26)	2.28	0.22–23.62	1
*DRB1*07:01*	1 (7.14)	6 (6.52)	1.1	0.12–9.91	1
*DRB1*01:02*	1 (7.14)	4 (4.35)	1.69	0.18–16.34	1
*DRB1*11:01*	1 (7.14)	5 (5.43)	1.34	0.14–12.38	1
*DRB1*01:01*	1 (7.14)	6 (6.52)	1.1	0.12–9.91	1

Table 6. Distribution of DQB1 HLA typing at the low-resolution level for patients diagnosed with bullous pemphigoid and controls

DQB1	Study participants, *n* (%)		Statistical processing		
	Patients	Control group	Odds ratio (OR)	Confidence interval (CI)	*p*
2	**17 (58.62)**	**32 (34.78)**	**2.65**	**1.13–6.24**	**0.039**
3	9 (31.03)	22 (23.91)	1.43	0.57–3.60	0.6
1	**2 (6.90)**	**31 (33.70)**	**0.15**	**0.03–0.65**	**0.01**
4	1 (3.45)	7 (7.60%)	0.43	0.05–3.68	0.72

Note. A statistically significant result is highlighted with a bold font.

obtained based on a significance of 5%, confidence interval, and *p*-value calculated using the χ^2 test (Table 7).

High-resolution distribution of HLA DQB1 class II alleles in the bullous pemphigoid group. At the high-resolution level, the HLA *DQB1*03:02* class II allele was significantly more common in the bullous pemphigoid group than in the control group ($p < 0.01$). For other types of HLA *DQB1*, no significant differences were found (Table 8).

High-resolution distribution of HLA DQB1 class II alleles in the SJS/TEN group. For all types of *DQB1* HLA typing, no significant results were registered at the high-resolution level in the SJS/TEN group (Table 9).

Study limitations

Given the extreme rarity of the dermatoses presented, a relatively small number of patients were enrolled in this study, which could have caused a selection bias. Thus, to eliminate potential errors, multicenter studies on a large sample of patients (≥1000 people) are necessary to confirm the present results. The case–control design may also be a limitation.

DISCUSSION

Genetic predisposition and various environmental factors are important in the onset of many autoimmune diseases. The major histocompatibility complex (MHC) is a highly polymorphic locus located on the short arm of chromosome 6 (6p21). MHC is an extremely significant component of the immune response [1]. Thus, a striking example is bullous pemphigoid, which is characterized by a loss of tolerance of the immune response to self-antigens. A certain set of so-called risk alleles was suggested to induce the dysregulation of autoimmunity while interacting with as-yet

Table 7. Distribution of *DQB1* HLA typing at the low-resolution level for patients diagnosed with Stevens-Johnson syndrome/toxic epidermal necrolysis and controls

DQB1	Study participants, *n* (%)		Statistical processing		
	Patients	Control group	Odds ratio (OR)	Confidence interval (CI)	*p*
2	7 (50.00)	32 (34.78)	1.875	0.6–5.82	0.42
3	4 (28.57)	22 (23.91)	1.27	0.36–4.46	0.96
1	2 (14.29)	31 (33.70)	0.33	0.07–1.56	0.25
4	1 (7.14)	7 (7.60)	0.93	0.1–8.22	1

Table 8. Distribution of *DQB1* HLA typing at the high-resolution level for patients diagnosed with bullous pemphigoid and controls

DQB1	Study participants, *n* (%)		Statistical processing		
	Patients	Control group	Odds ratio (OR)	Confidence interval (CI)	*p*
*DQB1*03:02*	**11 (37.93)**	**13 (14.13)**	**3.71**	**1.43–9.62**	**0.01**
*DQB1*05:03*	7 (24.14)	10 (10.87)	2.6	0.89–7.64	0.14
*DQB1*05:02*	3 (10.34)	12 (13.04)	0.77	0.20–2.94	0.95
*DQB1*06:03*	2 (6.90)	7 (7.60)	0.90	0.18–4.59	1
*DQB1*05:01*	1 (3.45)	9 (9.78)	0.33	0.04–2.72	0.49
*DQB1*04:02*	1 (3.45)	2 (2.17)	1.61	0.14–18.39	1
*DQB1*02:01*	1 (3.45)	4 (4.35)	0.79	0.08–7.32	1
*DQB1*06:04*	1 (3.45)	7 (7.60)	0.43	0.05–3.68	0.72
*DQB1*06:02*	1 (3.45)	0 (0)	-	-	-
*DQB1*02:02*	1 (3.45)	0 (0)	-	-	-

Note. A statistically significant result is highlighted with a bold font.

Table 9. Distribution of *DQB1* HLA typing at the high-resolution level for patients diagnosed with Stevens-Johnson syndrome/toxic epidermal necrolysis and controls

DQB1	Study participants, *n* (%)		Statistical processing		
	Patients	Control group	Odds ratio (OR)	Confidence interval (CI)	*p*
*DQB1*03:02*	5 (35.71)	13 (14.13)	3.38	0.98–11.67	0.1
*DQB1*05:03*	3 (21.43)	10 (10.87)	2.24	0.53–9.40	0.49
*DQB1*05:02*	1 (7.14)	12 (13.04)	0.51	0.06–4.28	0.85
*DQB1*06:03*	1 (7.14)	7 (7.60)	0.93	0.11–8.22	1
*DQB1*03:01*	1 (7.14)	18 (19.57)	0.32	0.04–2.58	0.45
*DQB1*02:01*	1 (7.14)	4 (4.35)	1.69	0.18–16.34	1
*DQB1*06:04*	1 (7.14)	7 (7.60)	0.93	0.11–8.22	1
*DQB1*02:02*	1 (7.14)	0 (0)	-	-	-

unknown environmental factors, leading to the formation of autoantibodies and initiation of autoimmune diseases [18].

Thus, HLA class II alleles are significant risk factors associated with antibody-mediated diseases. In bullous pemphigoid, the activation of antigen-specific B cells and secretion of antibodies depend on the interaction of T-cell receptors with classical MHC class II receptors [3]. Many studies have shown that the HLA *DQB1*03:01* allele predisposes to the development of bullous pemphigoid in various populations, including Iranian, German, Chinese, and American populations [6, 19–21]. In patients with the *HLA-DQB1*03:01* allele, T-cell tropism to various epitopes of BP180 antigens, particularly the BP180-NC16A domain, increased. This allele apparently plays one of the key roles in the presentation of antigens to T cells and activation of the immune response [19].

Interestingly, the *HLA-DQB1*03:02* and *HLA-DQB*04:01* alleles were associated with bullous pemphigoid in various Asian populations, particularly Japanese and Iranian [7, 20]. In this study, in patients with bullous pemphigoid at low- and high-resolution levels, *HLA-DRB1*14, DRB1*4,* and *HLA-DRB1*04:02* alleles were significantly more common (Tables 2 and 4). At the low-resolution level for *HLA-DQB1* alleles, the *DQB1*2* allele was significantly more common in these same patients, whereas *DQB1*1* can be considered protective for the Russian population (Table 6). At the high-resolution level, the *HLA-DQB1*03:02* allele was most often detected in patients with bullous pemphigoid than in healthy donors, which was consistent with data from studies in Asian populations (Table 8) [7, 20].

In the Chinese population, the *HLA-DRB1*10:01* allele was associated with bullous pemphigoid, whereas *DRB1*07:01* had a protective function [8].

In the Chinese population, H. Fang et al. [1] revealed a relationship between HLA class I alleles (*HLA-A*11:01* and *HLA-B*37:01*) and the onset of bullous pemphigoid.

HLA alleles of classes I and II are also significant in the development of severe drug-induced allergic reactions. Most drugs and their metabolites are prohaptens; therefore, they require certain immunogenicity through covalent binding

to carrier proteins (hapten antigen). Hapten antigens form a specific complex with HLA in antigen-presenting cells and then recognized by T-cell receptors [14, 22–25].

In SJS/TEN, different drug haptens were associated with different HLA allele variants. For example, in Taiwan, the *HLA-B*15:02* allele in patients with TEN was associated with the intake of anticonvulsants, particularly carbamazepine [26]. In addition, a definite association between the *HLA-B*58:01* allele and allopurinol-induced SJS/TEN has been found in many Asian populations [14–16, 22, 25, 27]. On the contrary, in abacavir-induced SJS, the *HLA-B*57:01* allele was detected [28, 29]. *HLA-A*11:01* and *HLA-B*13:01* alleles are factors increasing the risk of sulfanilamide-associated SJS and TEN in various Asian populations [30, 31]. However, in some cases, SJS/TEN can be associated with multiple HLA alleles. For example, phenytoin-induced SJS/TEN in the Malaysian population was associated not only with *HLA-B*15:02* but also with *HLA-B*15:13* alleles, and *HLA-B*15:13* can stimulate the development of phenytoin-induced DRESS syndrome [32].

In this study, at a low-resolution level, a significant increase in the incidence of the *HLA-DRB1*14* class II allele was registered in patients with SJS/TEN (Table 3). No protective alleles were identified, which may be due to the insufficiently large sample of patients.

Thus, further data on *HLA-DRB1* and *DQB1* class II alleles can be considered important differential diagnostic genetic biomarkers for severe bullous dermatoses in the Russian population. Considering the results of existing studies on the influence of HLA on the development of severe bullous dermatoses in other populations worldwide, the type and frequency of alleles presented in this study could contribute to the understanding of the development of the autoimmune response in these life-threatening diseases and identify possible similar pathogenetic aspects.

CONCLUSION

For the first time in the Russian population, we were able to identify *DRB1* and *DQB1* alleles characteristic of bullous pemphigoid and SJS/TEN at high- and low-resolution levels and detect HLA protective against bullous pemphigoid. However, major prospective studies in a larger sample of patients are warranted to estimate the incidence of other types of HLA alleles, particularly HLA class I alleles. According to scientific literature, genetic differences in susceptibility to severe bullous dermatoses persist across different ethnic groups in patients living outside their countries of ethnic origin, which emphasizes the importance of genetic factors in the development of these diseases. Moreover, detailed studies of the relationships were found between HLA and autoimmune and/or cytotoxic response of the immune system to various antigens in these complex diseases.

ADDITIONAL INFORMATION

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