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Short Communication

Distribution of HLA-A, -B, -C, -DRB1, -DQB1, -DPB1 allele frequencies in patients with COVID-19 bilateral pneumonia in Russians, living in the Chelyabinsk region (Russia)

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ABSTRACT

In this population-based case-control study conducted in the Chelyabinsk region of Russia, we examined the distribution of HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1, in a group of 100 patients with confirmed COVID-19 bilateral pneumonia. Typing was performed by NGS and statistical calculations were carried out with the Arlequin program. HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 alleles were compared between patients with COVID-19 and 99 healthy controls. We identified that COVID-19 susceptibility is associated with alleles and genotypes *rs9277534A* (disequilibrium with *HLA-DPB1*02:01*, *-02:02*, *-04:01*, *-04:02*, *-17:01* alleles) with low expression of protein products HLA-DPB1 ($p < 0.028$) and homozygosity at *HLA-C*04* ($p = 0.024$, $pc = 0.312$). Allele *HLA-A*01:01* was decreased in a group of patients with severe forms of bilateral pneumonia, and therefore it may be considered as a protective factor for the development of severe symptoms of COVID-19 ($p = 0.009$, $pc = 0.225$). Our studies provide further evidence for the functional association between HLA genes and COVID-19.

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1. Introduction

Since the beginning of the COVID-19 world-wide pandemic, the amino acid sequences of SARS-CoV-2 and HLA antigen interactions have been studied through *in silico* prediction models of spatial interactions between them [1,2]. While this allows prediction of the host immune response to viral antigens, such computational approaches should be considered with caution. For example, the *B*46:01* allele has shown the lowest binding capacity to the SARS-CoV-2 antigen repertoire and therefore can be considered as a marker of increased vulnerability to infection. On the contrary, the *B*15:03* allele is predicted to provide the host with a better ability to present conserved viral antigens to immune cells, which can be protective against the COVID-19 [1]. However, such relationships were not consistently confirmed when various cohorts from different countries were analyzed. In Italy, *HLA-B*44* and *-C*01* positively correlated with the expansion of COVID-19 [3]. Another Italian study showed a link between the presence of

*HLA-DRB1*15:01* ~ *DQB1*06:02*, *B*27:07* and severe symptoms of COVID-19 [4]. In the Canary Islands, alleles *HLA-A*11* and *HLA-C*01* as well as *HLA-DQB1*04* were found to be linked with higher COVID-19 mortality [5].

In Sardinia, extended haplotype *HLA-A*02:05* ~ *B*58:01* ~ *C*07:01* ~ *DRB1*03:01* was absent in all 182 patients indicating its protective function [6]. At the same time, the allele *HLA-C*04:01* and three-loci haplotype *HLA-A*30:02* ~ *B*14:02* ~ *C*08:02* were increased in COVID-19 patients, which suggests an association with the pathology [6].

Studies carried out in Asian populations also showed conflicting results. In a group of patients from Khan Province, a positive association between COVID-19 and the alleles *HLA-C*07:29* and *B*15:27* was found [7].

In a study of a large cohort of Israeli patients there was no correlation between the severity of the disease and any HLA alleles, the authors suggested that the existence of these gene variants do not play a role and are not risk factors in COVID-19 [8].

In a population from the United Arab Emirates, the alleles *HLA-B*51:01* and *HLA-A*26:01* were found to be negatively correlated with COVID-19 severity, while *HLA-A*03:01*, *HLA-DRB1*15:01* carri-

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ers, as well as B*44 supertype, were positively linked with pathology [9].

In a study in Moscow, Russia, the presence of allele *HLA-A*01:01* was linked to a higher risk of COVID-19 progression, whereas *HLA-A*02:01* and *HLA-A*03:01* were associated with a lower risk. The frequency of *HLA-A*01:01* was higher in young COVID-19 patient as opposed to the *HLA-A*02:01* homozygous' carriers cohort, where one patient died. Younger age mortality was correlated with homozygosity by the allele *HLA-A*01:01*, while in the *HLA-A*02:01* homozygous cohort only one patient died [10].

In the residents of the north-western part of Russia (Leningrad region), it was found that allele groups *A*02* and *A*26* decrease the probability of COVID-19 infection and *A*29* predisposes to the disease. HLA haplotypes that included allele group *A*02* were less frequent in COVID-19 patients, while in the general population these haplotypes are present at a much higher frequency [11].

Here we conducted a population-based study focusing on the link between classical HLA genes and the development of COVID-19-associated symptoms in the residents of the Chelyabinsk region (South Ural, Russia).

2. Materials and methods

100 patients of Chelyabinsk anticovid hospitals centres #2, 3, 9 were included in this study. All people had bilateral pneumonia of moderate and high severity (based on computed tomography scan confirming grade 1–2 pulmonary lesion). Diagnosis according to anamnesis data was confirmed by a SARS-CoV-2 RNA test through RT-PCR from a nasopharyngeal swab. The severity of the disease of the patients was analyzed retrospectively.

44 patients had a severe course of bilateral pneumonia according to the medical history and computed tomography (CT), while the rest were of moderate severity. All subjects were free of concomitant severe illness. All of them had positive IgG to SARS-CoV-2. (antibodies were determined using the kit SARS-CoV-2-Ig-EIA-BEST "Vector Best"™). Analysis was performed 2–6 months after recovery from SARS-CoV-2 confirmed by two negative PCR tests. The distribution of selected characteristics (sex and age) in Patients with Severe Bilateral Pneumonia caused by COVID-19 (cSBP), Bilateral Pneumonia caused by COVID-19 (cBP), and Healthy Subjects are presented in Table 1.

99 healthy individuals from the Chelyabinsk Regional Blood Bank served as healthy controls. None of them, according to anamnesis data, had COVID-19 from September 2020 to March 2021.

All persons included in the study, identified themselves of Russian ethnicity, and nationality was defined in the approved survey.

Typing was performed by NGS using the primer system «HLA-Expert», according to the manufacturer's instructions (DNA-technology, Moscow, Russia). Sequence analysis of the *HLA-A*, *-B*, *-C*, *-DRB1*, *-DQB1*, and *-DPB1* genes was performed by PCR amplification of exons 2, 3, 4 and the flanking intronic regions. Sequencing libraries were prepared with the "HLA-Expert" kit and the reactions included 1–5 ng genomic DNA (Protrans DNA BOX 500,

Germany). Sequencing was performed on a MiSeq machine using a MiSeq Reagent Kit v2 (500 cycles) (Illumina). Primary sequence data analysis (base-calling, trimming, filtering and alignment) was performed using "HLA-Expert" software. Alleles were denoted and annotated using an in-house developed software and the IMGT/HLA database.

2.1. Statistical analysis

Allele and genotype frequencies along with Hardy-Weinberg equilibrium and linkage disequilibrium in the controls and cases were analyzed using the Arlequin program (ver. 3.5.2.2) [12].

Continuous variables (age) were presented as median (between the minimum and maximum) for nonparametric distributions, and categorical variables (sex) were presented as frequencies (%). The significance associations among patients with Severe Bilateral Pneumonia caused by COVID-19 (cSBP), Bilateral Pneumonia caused by COVID-19 (cBP) and Healthy Subjects (HS) were evaluated using chi-square analysis or Fisher's exact test. The Mann-Whitney *U* test was used to analyze continuous variables.

Odds ratios (OR) with 95% confidence interval (CI) were calculated using the Chi-squared test for the comparison of the genotype and allele of single-nucleotide polymorphism (SNP) of the *HLA-DPB1* polymorphism (*rs9277534*) in the cSBP vs cBP study groups and groups of Healthy Subjects. Corrected *P*-values (*P_c*) were obtained by applying the Bonferroni correction. The significance was set at a level of 0.05. MedCalc for Windows version 12.7.7.0 (MedCalc Software, Ostend, Belgium) was used.

3. Results

Data shown in Table 2 indicate that the frequency of *HLA-A*01:01* was significantly lower in patients who developed severe COVID-19 disease compared to the healthy group. Therefore, the presence of this antigen could elicit a protective effect. We also found an increased homozygosity in the *HLA-C*04:01* allele in patients with severe symptoms (Table 2, Supplementary Fig. 2). However, all the above differences did not maintain significance after applying the Bonferroni correction. So distribution of *HLA-A*, *-B*, *-C*, *-DRB1*, *-DQB1* and *-DPB1* alleles was not found to be statistically different (Supplementary Table 1, Supplementary Figures 1, 3–7). No increase in homozygosity in *HLA-A*, *-B*, *-C*, *-DRB1*, *-DQB1* and *-DPB1* loci was found in those patients.

Interesting patterns were found when comparing the frequencies of the allelic variants for the SNP *rs9277534* (A/G) in the *HLA-DPB1* gene, which is known to be associated with high and low expression of the *DPB1* gene. It has been shown that the allele variant SNP *rs9277534A* is responsible for low expression of the gene in linkage disequilibrium with *HLA-DPB1*02:01*, *-02:02*, *-04:01*, *-04:02*, *-17:01*. At the same time, allele variant SNP *rs9277534G* is responsible for high gene expression in linkage disequilibrium with *HLA-DPB1*01:01*, *-03:01*, *-05:01*, *-06:01*, *-09:01*, *-10:01*, *-11:01*, *-13:01*, *-14:01*, *-15:01*, *-16:01*, *-19:01*,

Table 1

Distribution of selected characteristics (sex and age) in Patients with Severe Bilateral Pneumonia caused by COVID-19 (cSBP), Bilateral Pneumonia caused by COVID-19 (cBP) and Healthy Subjects (HS).

Characteristics	Number of subjects			p-value ^a	
	cSBP n = 44 (%)	cBP n = 56 (%)	Healthy Subjects n = 99 (%)	cSBP vs cBP vs	cSBP vs HS
Age: Median (min–max) ^c	42 (24–57)	42 (28–63)	36 (22–55)	p = 0.881 ^a	p = 0.056 ^a
Sex: Male	19 (43.18%)	29 (52%)	57 (57.58%)	p = 0.393 ^b	p = 0.112 ^b

^ap-values were calculated by Mann-Whitney test.

^bp-values were calculated by the chi-square test.

^cData were shown as median (min–max).

Table 2

The frequency and odds ratio values of the HLA alleles with uncorrected significant in Patients with Severe Bilateral Pneumonia caused by COVID-19 (cSBP) and Healthy Subjects (HS).

HLA	Number of subjects		Odds Ratios (OR)		
	cSBP	Healthy Subjects	cSBP vs HS		
	n = 44	n = 99	OR (95% CI)	p-value ^a	pc-value ^a
HLA-A*01:01 ^b	2 (0.02 ^b)	20 (0.10 ^b)	0.19 (0,04–0,84)	p = 0.009	pc = 0.225
HLA-C*04:01 (hom) ^c	5 (11.37% ^c)	2 (2.02% ^c)	6.22 (1,16–33,41)	p = 0.024	pc = 0.312

Abbreviations: HLA - human leukocyte antigen; SBP - Severe Bilateral Pneumonia; HS -Healthy Subjects; OR - odds ratio; CI - confidence interval; SNP - single nucleotide polymorphism.

^ap-values of χ^2 or Fisher's exact test before and after Bonferroni correction are shown, significant values are shown in bold, ^b gene frequency, ^c frequency of homozygous individuals.

–20:01 [13]. In COVID-19 patients, variant rs9277534A was found to be increased, as shown in Table 3.

4. Discussion

The contribution of the genetic components, including the HLA system, to the COVID-19 susceptibility has been shown in many genetic studies [14]. The *in silico* modeling predicted alleles with high (A*02:02, B*15:03, C*12:03) and low (B*46:01, A*25:01, C*01:02) ability for viral peptides presentation [1]. In the present study, we did not confirm the significance of these alleles in COVID-19 patients in Russians, living in the Chelyabinsk region. This shows that when planning experiments that consider molecular epidemiological data, one cannot rely solely on computational analysis data. Although the COVID-19 pandemic affected all countries and ethnic groups, a search for genetic predisposition did not yield consensus results between different ethnic groups due to HLA haplotypes variability. Distinct HLA alleles were determined predisposing for COVID-19, or no such correlation was found in different cohorts and ethnic groups. Our results obtained from ethnically homogenous group suggest that patients who were homozygous for the HLA-C*04:01 allele were at higher risk of severe COVID-19. Similar results have also been shown in multicentre studies in Europe [6,15]. According to these studies, HLA-C*04:01 is within the ten alleles providing the lowest binding affinity to viral peptides [2,15]. This may explain the higher susceptibility of C*04:01 carriers to infection within the European population.

In studies carried out in a Brazilian population [16], a higher susceptibility was shown for the individuals who were homozygous for the entire HLA-A locus.

Our data did not confirm previously published data regarding the association of HLA-A*01:01 with severe COVID-19, neither in

Russians nor European population [11,17]. On the contrary, our results suggest the HLA-A*01:01 allele might be protective against COVID-19 and severe symptoms.

Previously, it was shown that SNP rs9277534 regulated the expression of HLA-DP antigens affecting several important physiological and pathological pathways [18,19]. Spontaneous recovery from Hepatitis A virus infection in Asian and European individuals carrying the rs9277534A variant has previously been reported [20,21]. Furthermore, protection against Dengue fever was associated with allele G as well as the GG genotype [22]. Variant rs9277534G predisposes the autoimmune process in liver disease [23], as well as being associated with the outcome of hematopoietic stem cell transplantation [24].

In our study, we showed for the first time that HLA-DP expression can influence the progression of COVID-19. We hypothesize that this is indicated by a difference in the distribution of the rs9277534 SNP polymorphism, which is in linkage disequilibrium with HLA-DP alleles.

Our data showed that in COVID-19 patients, variant rs9277534A is increased (Table 3). As this SNP was significantly higher in patients who progressed to a severe COVID-19 disease, it might be directly linked to a lower antigen presentation [13]. The presence of the SNP rs9277534A is associated with lower HLA-DP antigen expression; supposedly this might impact the SARS-CoV-2-derived peptide repertoire that antigen presenting cells could process and present to the virus-specific CD4+ T-cells [13,25,26].

Therefore, the decrease in the presentation of viral antigens can be linked to more severe disease development. We believe that the effect associated with alternative HLA-DP expression may also be evident in COVID-19, facilitating viral clearance and reducing the risk of infection-associated immune complications.

Table 3

Distribution SNP polymorphism (rs9277534) in Patients with Severe Bilateral Pneumonia caused by COVID-19 (cSBP), Bilateral Pneumonia caused by COVID-19 (cBP) and Healthy Subjects (HS).

HLA-DPB1 SNP polymorphism (rs9277534)	Number of subjects			Odds Ratios (OR)			
	cSBP	cBP	Healthy Subjects	cSBP vs HS		cSBP vs cBP	
	n = 44 (%)	n = 56 (%)	n = 99 (%)	p-value ^a	OR (95% CI)	p-value ^a	OR (95% CI)
A (Low Exp)	75 (85.2%)	83 (74.1%)	143 (72.2%)	p = 0.014	2.22 (1.14–4.32)	p = 0.055	2.02 (0.98–4.16)
G (High Exp)	13 (14.8%)	29 (25.9%)	55 (27.8%)	pc = 0.028	0.45 (0.23–0.88)		0.5 (0.24–1.02)
AA	32 (72.7%)	29 (51.8%)	54 (54.5%)	p = 0.038	2.22 (1.03–4.81)	p = 0.032	2.48 (1.07–5.78)
GG + AG	12 (27.3%)	27 (48.2%)	45 (45.5%)	pc = 0.076	0.45 (0.21–0.97)	pc = 0.064	0.4 (0.17–0.94)
GG	1 (2.3%)	2 (3.6%)	10 (10.1%)	p = 0.105	0.21 (0.03–1.67)	p = 0.706	0.63 (0.06–7.16)
AG + AA	43 (97.7%)	54 (96.4%)	89 (89.9%)		4.83 (0.6–38.97)		1.59 (0.14–18.16)
AG	11 (25%)	25 (44.6%)	35 (35.4%)	p = 0.221	0.61 (0.27–1.35)	p = 0.041	0.41 (0.17–0.98)
GG + AA	33 (75%)	31 (55.4%)	64 (64.6%)		1.64 (0.74–3.64)	pc = 0.082	2.42 (1.02–5.73)

^ap-values of χ^2 or Fisher's exact test before and after Bonferroni correction are shown, significant values are shown in bold.

Abbreviations: HLA - human leukocyte antigen; SBP - Severe Bilateral Pneumonia, BP - Bilateral Pneumonia; HS -Healthy Subjects; OR - odds ratio; CI - confidence interval; SNP - single nucleotide polymorphism.

5. Conclusions

1. *HLA-C*04:01* homozygosity can be an important factor associated with COVID-19 in the Russian population of South Ural.
2. *HLA-A*01:01* can be protective against the development of severe symptoms of COVID-19
3. Polymorphism within the antigen binding group among different HLA antigens is less important for infection development than the level of expression of HLA-DP products. Individuals with low HLA-DP expression were found to be more susceptible to the COVID-19 infection.

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7. Authors' contributions

S.T.A., V.M.N., K.I.A. conception and study design. K.I.A., V.M.N., and E.A.E. performed the laboratory tests. S.D.S., B.S.V., V.M.N. analysis and interpretation. S.T.A. and A.G.S. compiled the data and wrote the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.humimm.2022.04.009>.

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