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BRIEF COMMUNICATION

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Distribution of HLA allele frequencies in 82 Chinese individuals with coronavirus disease-2019 (COVID-19)

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COVID-19 is a respiratory disease caused by a novel coronavirus and is currently a global pandemic. HLA variation is associated with COVID-19 because HLA plays a pivotal role in the immune response to pathogens. Here, 82 individuals with COVID-19 were genotyped for HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, and -DPB1 loci using next-generation sequencing (NGS). Frequencies of the *HLA-C*07:29*, *C*08:01G*, *B*15:27*, *B*40:06*, *DRB1*04:06*, and *DPB1*36:01* alleles were higher, while the frequencies of the *DRB1*12:02* and *DPB1*04:01* alleles were lower in COVID-19 patients than in the control population, with uncorrected statistical significance. Only *HLA-C*07:29* and *B*15:27* were significant when the corrected *P*-value was considered. These data suggested that some HLA alleles may be associated with the occurrence of COVID-19.

KEYWORDS

allele frequency, coronavirus disease-2019, Han population, HLA

A new type of pneumonia with an unknown causative agent broke out in Wuhan, Hubei province, China in late December 1, 2019.[1,2] A novel coronavirus was subsequently confirmed as the agent causing the disease.[1,2] The novel coronavirus was named 2019-nCoV by the World Health Organization (WHO) on January 12, 2020, and was later named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Classification Committee of Viruses on February 11, 2020.[3,4] Now, the associated disease has been named coronavirus disease 2019 (COVID-19) by the WHO.[3,4] The transmission mode for COVID-19 has been shown to be human to human.[3] COVID-19 is currently a global pandemic, and over 2 740 000 cases of COVID-2019 and 191 000 deaths have been reported globally as of April 24, 2020. The HLA system participates in immune regulation in humans and it plays an important role in the occurrence and development of infectious diseases.[5-7] Chen et al reported an odds ratio of 4.4 for SARS-CoV infection in individuals homozygous or heterozygous for *HLA-C*08:01*.[7] We hypothesized that HLA variation in the population may be associated with the occurrence of COVID-19, because HLA plays a pivotal role in the immune response to pathogens. Here, we report HLA allele frequencies in Chinese Han individuals with COVID-19 and a comparison between HLA allele distribution in COVID-19 patients and healthy individuals.

Eighty-two Han individuals from Zhejiang with confirmed COVID-19 were tested. All patients had mild or severe COVID-19, with none in a critical condition. Individuals were recruited for plasma donation after recovery and the plasma was used for treatment of other COVID-19 patients with severe or critical symptoms. The ages of the individuals ranged from 20 to 54. All samples were collected during the plasma donation process and informed consent was obtained from all individuals. The samples were genotyped at the HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, and -DPB1 loci by NGS-based typing, using an AllType NGS 9-Loci Amplification Kit (One Lambda Inc., Canoga Park, California), according to the manufacturer's instructions. HLA genotypes were assigned using TypeStream Visual Software version 2.0 (One Lambda Inc.). The Chinese HLA common and well-documented principle

was used to solve ambiguous HLA allele combination assignments.[8] Hardy-Weinberg equilibrium (HWE) was assessed by maximum likelihood, using the method of Guo and Thompson, which has been implemented in Arlequin version 3.5.[9] Odds ratios (95% confidence interval [CI]) and *P*-values were calculated using Fisher's exact test or Yates continuity-corrected χ^2 test in Prism 5.0 software (GraphPad, San Diego, California). Corrected *P*-values (*Pc*) were obtained by multiplying the number of alleles at each locus using the Benjamini-Hochberg method. The significance of the *Pc*-value was set at a level of .05.

The results of HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, and -DPB1 genotyping were fitted for HWE after considering the *Pc*-value (Table S1). The rates of ambiguous HLA allele combinations for HLA-A, -B, -C, -DRB1, -DRB3/4/5,-DQA1, -DQB1, -DPA1, and -DPB1 loci were 1.22%, 3.66%, 3.66%, 47.56%, 6.10%, 1.22%, 47.56%, 1.22%, and 46.34%, respectively. The number of alleles at the HLA-A, -C, -B, -DRB1, -DRB3/4/5, -DQA1 -DQB1, -DPA1, and -DPB1 loci were 15, 20, 30, 25, 9, 13, 14, 5, and 15, respectively (Table S2). The allele distributions of HLA-A, -C, -B, -DRB1, -DQB1, and -DPB1 loci were compared between COVID-19 patients and control individuals. The resulting ORs (95% CI) and *P*-values are presented in Table S2. Data for control individuals were obtained from our previous studies of bone marrow donors in the Zhejiang Han population.[10,11] There were 3548 individuals in the control group with genotyping data for the HLA-A, -B, -C, -DRB1,-DQB1 loci, and 242 with data for HLA-DPB1 locus.[10,11] HLA genotyping of the control individuals was performed using polymerase chain reaction at two-field resolution, as in our previous reports.[10,11] The frequencies and ORs of the HLA alleles, with uncorrected significance, for COVID-19 patients are listed in Table 1. *HLA-C*07:29*, *C*08:01G* (including *C*08:01* and *C*08:22*), *B*15:27*, *B*40:06*, *DRB1*04:06*, and *DPB1*36:01* frequencies were higher in COVID-19 patients than in the control population, with uncorrected statistical significance ($P < .05$). The ORs were 130.20, 1.65, 3.59, 2.43, 2.39, and 12.08, respectively. Meanwhile, the frequencies of the *DRB1*12:02* and *DPB1*04:01* alleles were significantly lower in COVID-19 patients ($Pc < .05$), with ORs of 0.44 and 0.40, respectively. However, only the frequencies of *HLA-C*07:29* and *B*15:27* remained significantly different after *P*-value correction. The *HLA-C*07:29* allele is a well-documented allele in the Chinese population, with five cases in the 816 486 bone marrow donors.[8] In the present study, *HLA-C*07:29* was found in one COVID-19 patient, but in no individuals in the control group. Therefore, the significance of *C*07:29* should be interpreted with caution and this result needs to be confirmed in further studies with larger sample sizes.

Two alleles, *B*07:02* (1.38%) and *B*27:04* (1.92%), with frequencies greater than 1% in the control group, were not found in COVID-19 patients. The odds ratios for *B*07:02* and *B*27:04* were 0.216 (95% CI: 0.01335-3.494, $P = .2408$) and 0.155 (95% CI: 0.009598-2.503, $P = .134$). Because there were no data for HLA-DRB3/4/5, -DQA1, or -DPA1 loci in the control group,[10,11] the allele frequencies of these loci could not be compared between the two groups. The allele frequency data for the HLA-DRB3/4/5, -DQA1, and -DPA1 loci are summarized in Table S3.

The HLA system is an important host genetic factor that plays an important role in determining the outcome of many infectious diseases, including human immunodeficiency virus (HIV) and severe acute respiratory syndrome (SARS).[6,12,13] Associations between HLAs and the development and/or severity of SARS have been found in some populations.[7,13,14] *HLA-B*07:03*, *B*46:01*, *DRB1*03:01*, *DRB1*12:02* alleles have been reported to be associated with susceptibility to SARS, but some studies have

TABLE 1 The frequency and odds ratio values of the HLA alleles with uncorrected significant in COVID-19 individuals

	COVID-19		Control group				
Allele	**N**	**Frequency (%)**	**N**	**Frequency (%)**	**Odds ratio (95% CI)**	***P*-value**	***Pc*-value**
*C*07:29*	1	0.61	0	0	130.20 (5.28-3211)	**.001**	**.025**
*C*08:01G#*	23	14.02	640	9.02	1.65 (1.05-2.58)	.039	.371
*B*15:27*	8	4.88	100	1.41	3.59 (1.72-7.50)	**.001**	**.030**
*B*40:06*	11	6.71	204	2.87	2.43 (1.30-4.55)	.009	.129
*DRB1*04:06*	12	7.32	227	3.20	2.39 (1.3-4.36)	.007	.173
*DRB1*12:02*	8	4.88	750	10.57	0.43 (0.21-0.89)	.026	.324
*DPB1*04:01*	8	4.88	55	11.36	0.40 (0.19-0.86)	.023	.174
*DPB1*36:01*	4	2.44	1	0.21	12.08 (1.34-108.9)	.021	.174

Note: *#C*08:01G (9.02%)* was included *C*08:01* and *C*08:22*. The number of the individuals in the control group were 3548 for HLA-B, -C, -DRB1 loci, and 242 for HLA-DPB1 locus.

not confirmed these results.[15] The sequence of SARS-CoV-2 shows some homology with SARS-CoV, but there are distinct differences between the two viruses.[4] Therefore, the association of HLA alleles with COVID-19 warrants further research.[15,16] In the present study, these SARS-susceptibility alleles were not found to occur at a significantly different frequency in COVID-19 patients after *P*-value correction. Nguyen et al[16] predicted the binding affinity of SARS-CoV-2 to 145 HLA class I alleles, and *HLA-A*02:02*, *HLA-B*15:03*, and *HLA-C*12:03* were found to be the top presenters of conserved peptides. We found that *B*15:27* alleles may be associated with the occurrence of COVID-19. *HLA-B*15:03* and *B*15:27* belong to the *B*15* group and have 10 nucleotide differences. Prediction of the peptide-binding groove of these alleles may help to explain their association with COVID-19. Although the number of samples in the present study was small, these data will still be useful for exploring the influence of HLA gene polymorphisms on susceptibility to COVID-19 and patient outcomes.

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CONFLICT OF INTEREST

The authors have declared no conflicting interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Wu JT, Leung K, Bushman M, et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan. *China Nat Med*. 2020;26:506-510.
2. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: an overview. *J Chin Med Assoc*. 2020;83:217-220.
3. Stower H. Spread of SARS-CoV-2. *Nat Med*. 2020;26:465.
4. Xu J, Zhao S, Teng T, et al. Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-CoV. *Viruses*. 2020;12:244.
5. Dendrou CA, Petersen J, Rossjohn J, Fugger L. HLA variation and disease. *Nat Rev Immunol*. 2018;18:325-339.
6. Bardeskar NS, Mania-Pramanik J. HIV and host immunogenetics: unraveling the role of HLA-C. *HLA*. 2016;88:221-231.
7. Chen YM, Liang SY, Shih YP, et al. Epidemiological and genetic correlates of severe acute respiratory syndrome coronavirus infection in the hospital with the highest nosocomial infection rate in Taiwan in 2003. *J Clin Microbiol*. 2006;44:359-365.
8. He Y, Li J, Mao W, et al. HLA common and well-documented alleles in China. *HLA*. 2018;92:199-205.
9. Excoffier L, Lischer HE. Arlequin suite ver 3.5: a new series of programs to perform population genetics analyses under Linux and windows. *Mol Ecol Resour*. 2010;10:564-567.
10. Chen N, Wang W, Wang F, et al. The distributions of HLA-A, HLA-B, HLA-C, HLA-DRB1 and HLA-DQB1 allele and haplotype at high-resolution level in Zhejiang Han population of China. *Int J Immunogenet*. 2019;46:7-16.
11. He Y, Tao S, Zhang W, et al. Establishment of a polymerase chain reaction sequencing based typing method for HLA-DPB1 exons 2 and 3 and investigation of their polymorphisms. *Chin J Med Genet*. 2015;32:40-43.
12. Xiong P, Zeng X, Song MS, et al. Lack of association between HLA-A, -B and -DRB1 alleles and the development of SARS: a cohort of 95 SARS-recovered individuals in a population of Guangdong, southern China. *Int J Immunogenet*. 2008;35:69-74.
13. Lin M, Tseng HK, Trejaut JA, et al. Association of HLA class I with severe acute respiratory syndrome coronavirus infection. *BMC Med Genet*. 2003;4:9.
14. Wang SF, Chen KH, Chen M, et al. Human-leukocyte antigen class I Cw 1502 and class II DR 0301 genotypes are associated with resistance to severe acute respiratory syndrome (SARS) infection. *Viral Immunol*. 2011;24:421-426.
15. Sanchez-Mazas A. HLA studies in the context of coronavirus outbreaks. *Swiss Med Wkly*. 2020;150:w20248.
16. Nguyen A, David JK, Maden SK, et al. Human leukocyte antigen susceptibility map for SARS-CoV-2. *J Virol*. 2020; JVI.00510-20. https://doi.org/10.1128/JVI.00510-20.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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