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On the peptide binding affinity changes in population-specific HLA repertoires to the SARS-CoV-2 variants Delta and Omicron

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ABSTRACT

Objective: To investigate the changes of Spike protein-HLA binding affinity profiles between the Wuhan strain and two dominant variants, the Delta and the Omicron strains, among the Taiwanese, the British and the Russian populations.

Methods: The HLA frequencies and the HLA-peptide binding affinity profiles in the T-CoV database were combined to conduct the study. We focused on the public alleles in the three populations (HLA-A, HLA-B, HLA-C, HLA-DRB1, and/or HLA-DPA1/DPB1 alleles) and the altered peptides of the spike protein (compared to the Wuhan strain) in the Delta G/478K·V1 (B.1.617.2 + AY.1 + AY.2) and the Omicron (BA.1) strains.

Results: For the Delta strain, tight bindings of the altered peptides to the HLA alleles decrease in all three populations and almost vanish in the Taiwanese population. For the Omicron strain, tight bindings are mostly preserved for both HLA classes and in the Taiwanese and the British populations, with a slight reduction in HLA class II in the Taiwanese (1.4%), while the Russian population preserves a relatively high fraction of tight bindings for both HLA classes.

Conclusion: We comprehensively reported the changes in the HLA-associated SARS-CoV-2 Spike protein peptide binding profiles among the Taiwanese, the British, and the Russian populations. Further studies are needed to understand the immunological mechanisms and the clinical value of our findings.

1. Introduction

The COVID-19 (SARS-CoV-2) pandemic had broken out in December 2019 and continues to spread worldwide. Until May 2022, a total of 500 million confirmed cases and six million deaths has been reported [1]. During this pandemic, several variants of SARS-CoV-2 have been identified to be highly transmissible and capable of immune evasion, including the Alpha (B.1.1.7), Delta (B.1.617.2), and Omicron (B.1.1.529) strains [2–4]. Although a significant portion of world population has received vaccination, breakthrough infections by the variants have become more and more common. Such endless appearance of mutated variants and their ability to evade immune defense has posed a

Abbreviations: SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COVID-19, Coronavirus disease 2019; MHC, Major histocompatibility complex; HLA, Human leukocyte antigen; pMHC, Peptide-MHC; TCR, T-cell receptor; T-CoV, T-cell COVID-19 Atlas.

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serious threat to the public health and the economy of the entire world.

From the public health records and the clinical reports, it appears that the susceptibility and the severity of SARS-CoV-2 vary across regions and countries. Several factors have been documented to associate with this variation, such as the policies of isolation and quarantine, the strategies of vaccination, and the social determinants of health [5,6]. In addition, genetic variations, especially in the region of major histocompatibility complex (MHC), are suggested to be crucial [7]. The MHC contains a large set of closely linked polymorphic genes encoding cell surface proteins responsible for the adaptive immune responses, with the leukocyte antigen (HLA) as the corresponding human version. To recognize and defend these variants, the key is the HLA polymorphisms implemented in our genome, particularly for HLA class II, the subtype responsible for the initiation of humoral immunity. Following this line of rationales, the first thing we can consider is the general trend of the strong binding profile: the loss (gain) of strong bindings indicates a weaker (stronger) ability to recognize virial variants through HLA class II molecules. The second thing is the presence or absence of certain HLA class II alleles, as they might associate with the severity of clinical outcomes or the epidemic patterns. Indeed, several HLA class II alleles has been reported to be associated with the severity of SARS-CoV-2, including the allele HLA-DRB1*04 [8,9] and HLA-DRB1*08:02 [10]. Anzurez et al. also reported an association of the allele HLA-DRB1*09:01 with the severity but not the susceptibility of SARS-CoV-2 infection in the Japanese population [11]. These reports support the idea that HLA class II serves as the first line of defense against SARS-CoV-2 and its polymorphisms are linked to the variation of disease severity. Besides HLA class II, viral peptides can be presented by HLA class I molecules (e.g., HLA-A, HLA-B, and HLA-C) to activate cytotoxic CD8 T cells, thereby removing the virus-infected cells. In this regard, just as important as HLA class II, the presence or absence of certain HLA class I alleles might be connected to the clinical outcomes and the epidemic patterns of SARS-CoV-2 infection. Consistent with this idea, Weiner et al. showed that HLA-C *04:01 is a potential risk allele for the SARS-CoV-2 infection as it is associated with severe clinical outcomes (such as intubation) in European patients [12]. Similarly, a sex-dependent association of HLA-C *04:01 with COVID-19 severity was observed in the Armenian population [13]. A possible explanation is that possessing HLA-C *04:01 allele leads to a higher viral load, as shown in a study of SARS-induced pneumonia [14].

From the molecular perspective, the diversity of immune responses against the pathogens could be in part attributed to the variation of antigen-HLA binding affinity and specificities across the biological races of humans. By applying *in-silico* approaches, several reports have shown that the diverse epidemic patterns of SARS-CoV-2 infection were associated with HLA polymorphisms [15,16]. Most studies mentioned above were based on the Wuhan strain of SARS-CoV-2. In the presence of multiple SARS-CoV-2 variants as currently it stands, the binding affinity profiles might vary significantly, leading to different clinical outcomes and epidemic patterns [17]. In this case, application of *in-silico* prediction is able to deal with the changing binding profiles between virus antigen and HLA alleles more immediately. Recently, T-cell COVID-19 Atlas (T-CoV) database has been established to characterize the changes of binding profiles between the Wuhan strain and the other variants [18]. This database provides a global and comprehensive view on the SARS-CoV-2 mutational profiles. What is lacking, however, is the exploration of these profiles with respect to the biological races of humans, which could serve as a potential way to explain the epidemic patterns varying across populations. Herein, we investigate and compare the changes of binding affinity profiles between the Wuhan strain and two dominant variants, the Delta and the Omicron strains, in an Asian group, the Taiwanese population, and two European groups, the British population and the Russian population. The goal is to explore whether the HLA polymorphisms of these populations lead to different predictions of SAR-CoV-2 susceptibility and should be taken into account when implementing the public health rules and policies.

2. Material and methods

2.1. Data resources

The profiles of binding affinities between SARS-CoV-2 peptides and HLA alleles were obtained from the T-COV database (https://t-cov.hse.ru), which contained large-scale *in silico* simulation data of binding affinities between the SARS-CoV-2 variants and the worldwide HLA alleles [18]. As for the profiles of HLA alleles in the Taiwanese, British, and Russian populations, we obtained from the Taiwan Biobank, a study conducted in the British population, and the Federal Register of Bone Marrow Donors, respectively [19,20].

2.2. HLA allele profiles

To make the HLA profiles comparable between the Taiwanese population and the British population, we selected their public HLA genes, namely, *HLA-A*, *HLA-B* and *HLA-C* for HLA class I, and *HLA-DRB1, HLA-DPA1/DPB1* for HLA class II. Regarding the HLA profiles Russian population, only the *HLA-A*, *HLA-B* and *HLA-C* for HLA class I, and *HLA-DRB1* for HLA class II were available for further generalization. To simplify the analyses, only HLA alleles or haplotypes of frequencies $\geq$0.05 were chosen for the study.

2.3. Selection of binding affinities profiles

The Wuhan variant was set as the reference in the T-COV database and in this study, by which we compared the changes in the Delta G/478K·V1 (B.1.617.2 + AY.1 + AY.2) and the Omicron (BA.1) strains. Motivated by the reported immune escape scenarios of the spike mutations [3], we focused on the mutated viral peptides in the spike protein, and analyzed their binding affinities to the HLA profiles in the Taiwanese, the British and the Russian populations.

2.4. Analysis and data visualization

All the analysis was conducted using R software (version 4.1.1). The Distribution plots and bar plots were obtained using ggplot2 (version 3.3.5). The alluvial diagrams were illustrated using ggalluvial (version 0.12.3) and weighted with the *frequency score* below:

$$frequency\ score_i = allele\ frequency_i \times 10, rounding\ to\ integer$$

3. Results

3.1. Overview of analysis, design and implementation process

Fig. 1 illustrates the design of the current study and lists the parameters used for our analyses. The flowchart shown in Fig. 1 lists the total number of the common HLA alleles, the altered peptides in the Spike protein, and the pairings of altered peptide-common HLA alleles used in this study. Among them, 27 HLA alleles with frequency $\geq$0.05 in the Taiwanese population, 29 HLA alleles from 5 public HLA genes in the British population, and 27 HLA alleles from 4 available HLA genes in the Russian population were defined as the common HLA alleles. The details of these HLA alleles were summarized in Table 1. For these common alleles, the binding affinities to the 142 and 2453 altered peptides in the Delta and the Omicron strains, respectively, were used to characterize the changes of peptide-HLA binding affinity profile in the Taiwanese population. Likewise, the binding affinities to the 240 (in the Delta) and 2694 (in the Omicron) altered peptides, and the binding affinities to the 242 (in the Delta) and 2497 (in the Omicron) altered peptides were used to conduct the analyses in the British and the Russian populations, respectively.

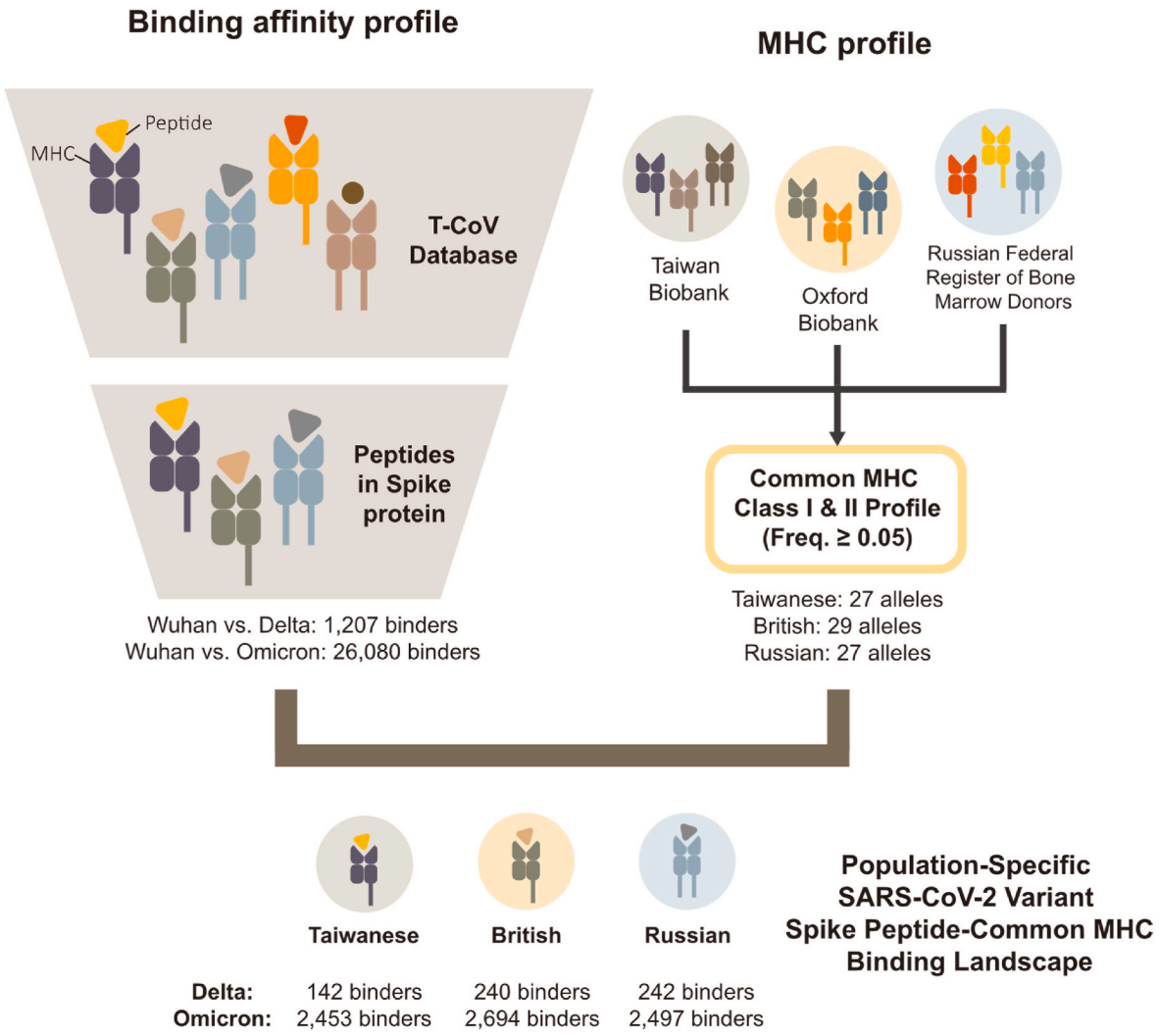

Fig. 1. Overview of the study design.

Table 1
Overview of the common HLA alleles included between the Taiwanese, the British and the Russian populations.

	HLA-A	HLA-B	HLA-C	HLA-DRB1	HLA-DPA1/DPB1
Common alleles in the Taiwanese population	HLA-A*11:01	HLA-B*40:01	HLA-C*07:02	HLA-DRB1*09:01	HLA-DPA1*02:02/DPB1*05:01
	HLA-A*24:02	HLA-B*46:01	HLA-C*01:02	HLA-DRB1*12:02	HLA-DPA1*01:03/DPB1*02:01
	HLA-A*33:03	HLA-B*58:01	HLA-C*03:04	HLA-DRB1*11:01	HLA-DPA1*01:03/DPB1*04:01
	HLA-A*02:07	HLA-B*13:01	HLA-C*03:02	HLA-DRB1*15:01	HLA-DPA1*02:02/DPB1*02:02
	HLA-A*02:01		HLA-C*08:01	HLA-DRB1*03:01	
	HLA-A*02:03		HLA-C*03:03	HLA-DRB1*08:03	
				HLA-DRB1*04:05	
Common alleles in the British population	HLA-A*02:01	HLA-B*08:01	HLA-C*07:01	HLA-DRB1*07:01	HLA-DPA1*01:03/DPB1*04:01
	HLA-A*01:01	HLA-B*07:02	HLA-C*07:02	HLA-DRB1*03:01	HLA-DPA1*01:03/DPB1*02:01
	HLA-A*03:01	HLA-B*44:02	HLA-C*05:01	HLA-DRB1*15:01	HLA-DPA1*01:03/DPB1*04:02
	HLA-A*24:02	HLA-B*15:01	HLA-C*06:02	HLA-DRB1*04:01	HLA-DPA1*01:03/DPB1*03:01
	HLA-A*11:01	HLA-B*40:01	HLA-C*04:01	HLA-DRB1*01:01	
		HLA-B*44:03	HLA-C*03:04	HLA-DRB1*13:01	
		HLA-B*35:01	HLA-C*03:03		
Common alleles in the Russian population	HLA-A*02:01	HLA-B*07:02	HLA-C*07:01	HLA-DRB1*07:01	–
	HLA-A*03:01	HLA-B*44:02	HLA-C*04:01	HLA-DRB1*15:01	–
	HLA-A*01:01	HLA-B*08:01	HLA-C*07:02	HLA-DRB1*03:01	–
	HLA-A*24:02	HLA-B*18:01	HLA-C*12:03	HLA-DRB1*01:01	–
	HLA-A*26:01	HLA-B*35:01	HLA-C*06:02	HLA-DRB1*11:01	–
	HLA-A*11:01	HLA-B*13:02	HLA-C*02:02	HLA-DRB1*13:01	–
		HLA-B*51:01	HLA-C*03:04	HLA-DRB1*11:04	–

Common HLA alleles were defined as the alleles with frequency ≥ 0.05.

3.2. Distribution of common HLA allele frequencies across populations

To proceed, we first compared the frequencies of the common HLA alleles in the three populations. Distinct frequency patterns were observed between the Taiwanese and the British populations (Supplementary Fig. 1). For example, HLA-A*01:01, HLA-A*03:01, HLA-B*08:01, HLA-C*07:01, and HLA-DPA1*01:03/DPB1*04:01 were found to carry the highest frequencies in the British population but not in the Taiwanese population. Likewise, the predominant HLA alleles in the Taiwanese population are HLA-A*11:01, HLA-A*24:02, HLA-B*40:01, HLA-C*07:02, HLA-DRB1*09:01, and HLA-DPA1*02:02/DPB1*05:01, while HLA-A*02:01, HLA-B*08:01, HLA-C*07:01, HLA-DRB1*03:01, and HLA-DPA1*01:03/DPB1*04:01 are predominant in the British population. Nevertheless, both populations possess HLA-C*07:02 as a common HLA allele (Supplementary Fig. 1C). In comparison, similar frequency patterns were observed between the British population and the Russian population (Supplementary Fig. 2). Such similarity is compatible with their largely shared common HLA alleles (Table 1).

3.3. Comparison of binding affinity changes of the delta variant among the Taiwanese, the British and the Russian populations

We next computed the peptide-HLA binding affinity changes between the reference peptides (from the Wuhan strain) and the altered/mutated peptides (from the Delta strain). A sign test (i.e., the exact binomial test) on the binding affinity change was conducted for the Taiwanese population. The p-values were computed for two-side test on a null hypothesis that the mutation has an equal chance to make the binding affinity stronger or weaker. For the Delta variant, we found that binding affinity changes to the HLA class I or class II alleles were not significant (two-side p-value = 0.39 for HLA class I alleles, and two-side p-value = 0.26 for HLA class II alleles; both are larger than alpha = 0.05). Despite these insignificant changes, the Taiwanese population shows a decrease of tight bindings (yellow color) from the reference peptides to the altered peptides for both HLA class I and class II alleles (4.1%–0% and 1.5%–0%, respectively, Fig. 2C and D). By contrast, the fraction of moderate bindings increases from 46.9% to 71.4% for the HLA class I alleles and from 54.4% to 64.7% for the HLA class II alleles, respectively (Fig. 2C and D). In the British population, a decrease of tight bindings (yellow color) for the HLA class I alleles was also found (from 11.1% to 4.4%), while the change of tight bindings is minor for the HLA class II alleles (Fig. 3C and D). Of note, tight bindings to the altered peptides (yellow color) only appear in the British population but not in the Taiwanese population. As for the fraction of moderate bindings to the altered peptides, the British population possess less than the Taiwanese population for the HLA class I alleles (28.9% vs. 71.4%, Figs. 2C and 3C) but more than the Taiwanese population for the HLA class II alleles (92.7% vs. 64.7%, Figs. 2D and 3D).

For the Russian population, we found a reduction of tight bindings to both HLA class I and class II alleles (Fig. 4C and D). Other than that, the patterns are similar to those found in the British population but not the Taiwanese population. For example, for the HLA class I alleles, the Russian population has 5.3% of tight bindings and 31.6% of moderate bindings and the British population has 4.4% of tight bindings and 28.9% of moderate bindings, while the Taiwanese population has zero

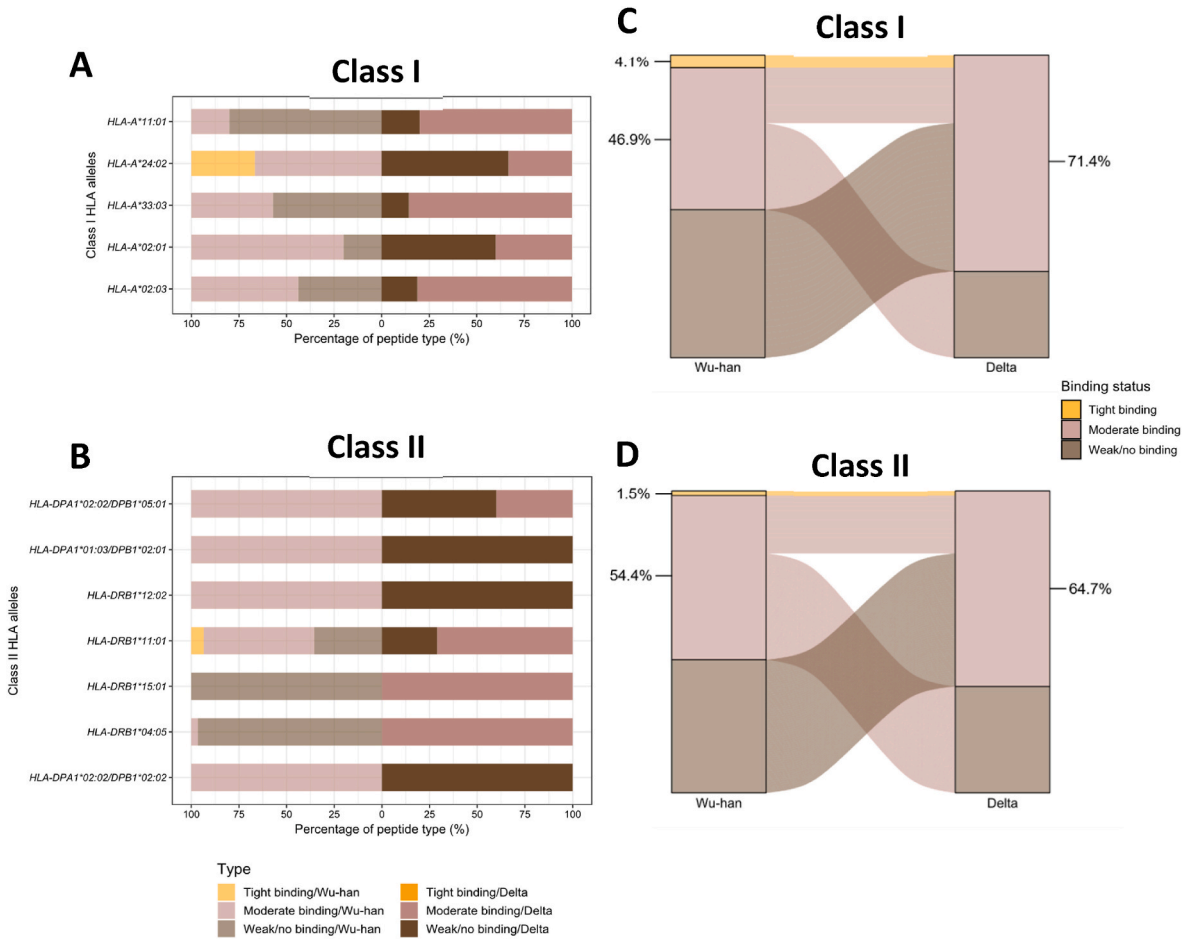

Fig. 2. Overview of binding affinity profiles changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Delta variant in the Taiwanese population.

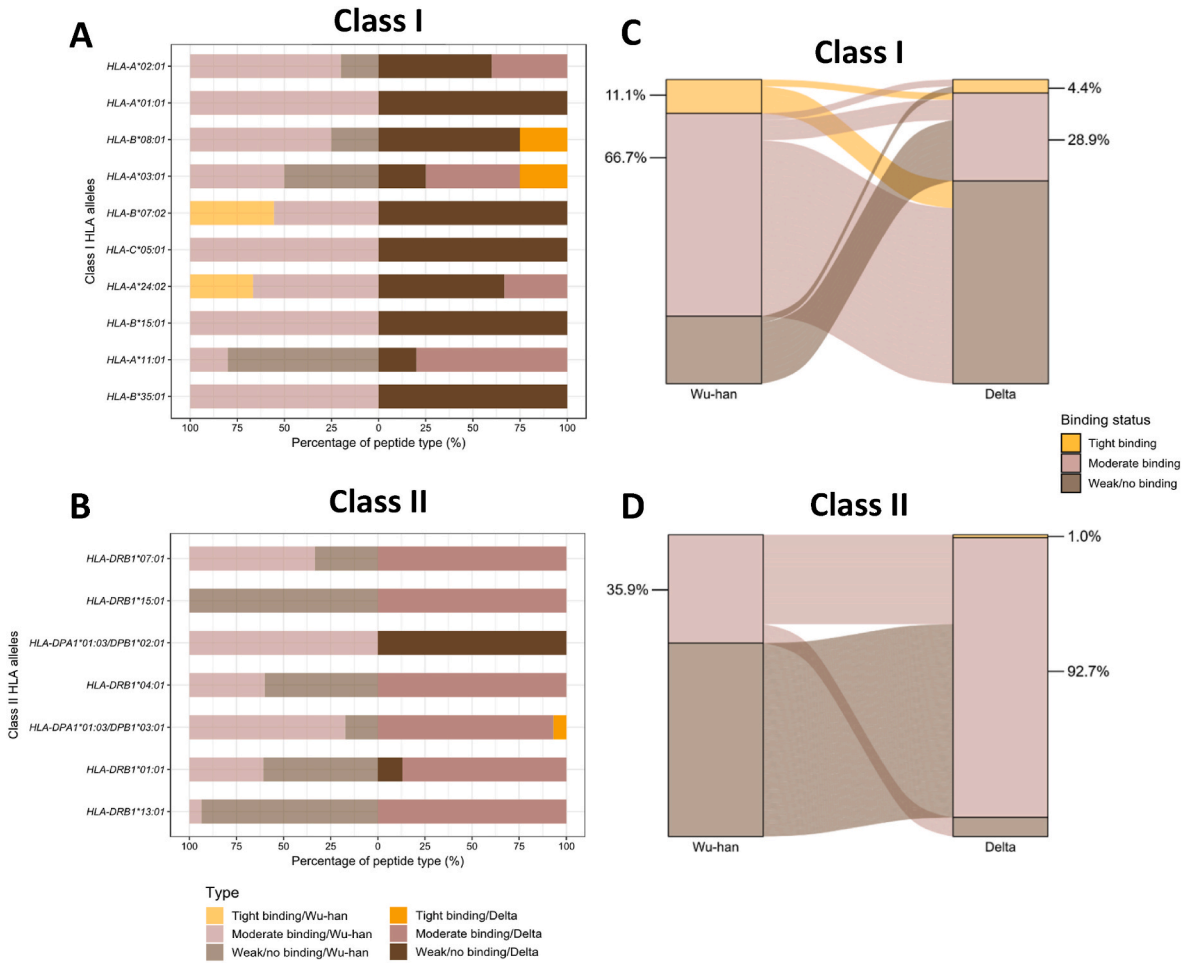

Fig. 3. Overview of binding affinity profiles changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Delta variant in the British population. (A, B) Detailed binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Delta variant in the British population, separately for (A) class I HLA alleles and (B) class II HLA alleles. (C, D) Overall binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Delta variant in the British population, separately for (C) class I HLA alleles and (D) class II HLA alleles.

tight bindings and 71.4% of moderate bindings. Likewise, for the HLA class II, the Russian population shows 0.5% of tight bindings and 90.0% of moderate bindings and the British population shows 1% of tight bindings and 92.7% of moderate bindings, while the Taiwanese shows zero tight bindings and 64.7% of moderate bindings (Figs. 2–4).

3.4. Comparison of binding affinity changes of the Omicron variant among the taiwanese, the British and the Russian populations

We used the similar approach to compute and compare the HLA-peptide binding affinity changes from the Wuhan strain to the Omicron strain. A sign test was first conducted for the Taiwanese population. Different from the Delta strain, the sign test for the Omicron strain showed significant changes in binding affinities for both HLA class I and class II alleles (two-side p-value $= 2.93\times10^{-5}$ for HLA class I alleles, and two-side p-value $= 2.91 \times 10^{-14}$ for HLA class II alleles; both are smaller than alpha $= 0.05$). In the Taiwanese population, we also found a slight reduction of the tight bindings for the HLA class II alleles (1.9%–1.4%) but not for the HLA class I alleles (Fig. 5C and D). Nevertheless, the fraction of moderate bindings increases for both HLA class I and class II alleles (40.9%–66.5% and 54.9%–60.3%, respectively, Fig. 5C and D). The details are listed in Fig. 5B. For example, tight bindings are reduced in the *HLA-DRB1*03:01* and *HLA-DRB1*15:01* alleles. A similar trend of the changes in the moderate bindings for the HLA class I alleles was observed between the British and the Taiwanese populations. Both show a slight increment (40.9%–66.5% in the Taiwanese population and 48.7%–54.4% in the British population, Figs. 5C and 6C). As for the HLA class II alleles, while the Taiwanese population shows an increment from 54.9% to 60.3%, the British population has a slight reduction from 58.7% to 57.7% (Figs. 5D and 6D). The trends of the changes in the tight bindings are different between these two populations. For the HLA class I alleles, the Taiwanese population maintains the same fraction of tight bindings (from 6.1% to 6.1%), while the British population shows a nearly one-fold reduction (from 8.2% to 4.2%, Figs. 5C and 6C). Conversely, for the HLA class II alleles, the Taiwanese population shows a nearly 25% of reduction (from 1.9% to 1.4%), whereas the British population has a slight increment (from 3.8% to 3.9%, Figs. 5D and 6D).

Despite the similarity of the binding affinity changes with the British population in the Delta strain, the Russian population shows different patterns from the British population in the Omicron strain. This difference is particularly manifested in the changes of tight bindings. For the HLA class I alleles, the Russian population maintains the highest fraction among all the three populations (from 8.4% to 7.8%, Fig. 7C). Similarly, for the HLA class II alleles, the Russian population holds the highest fraction (from 4.9% to 5.4%, Fig. 7D). As for the moderate bindings, the Russian population exhibits a similar increasing trend as the Taiwanese population, i.e., from 41.6% to 58.4% for the HLA class I alleles and from 53.5% to the 64.2% for the HLA class II alleles (Fig. 7C and D).

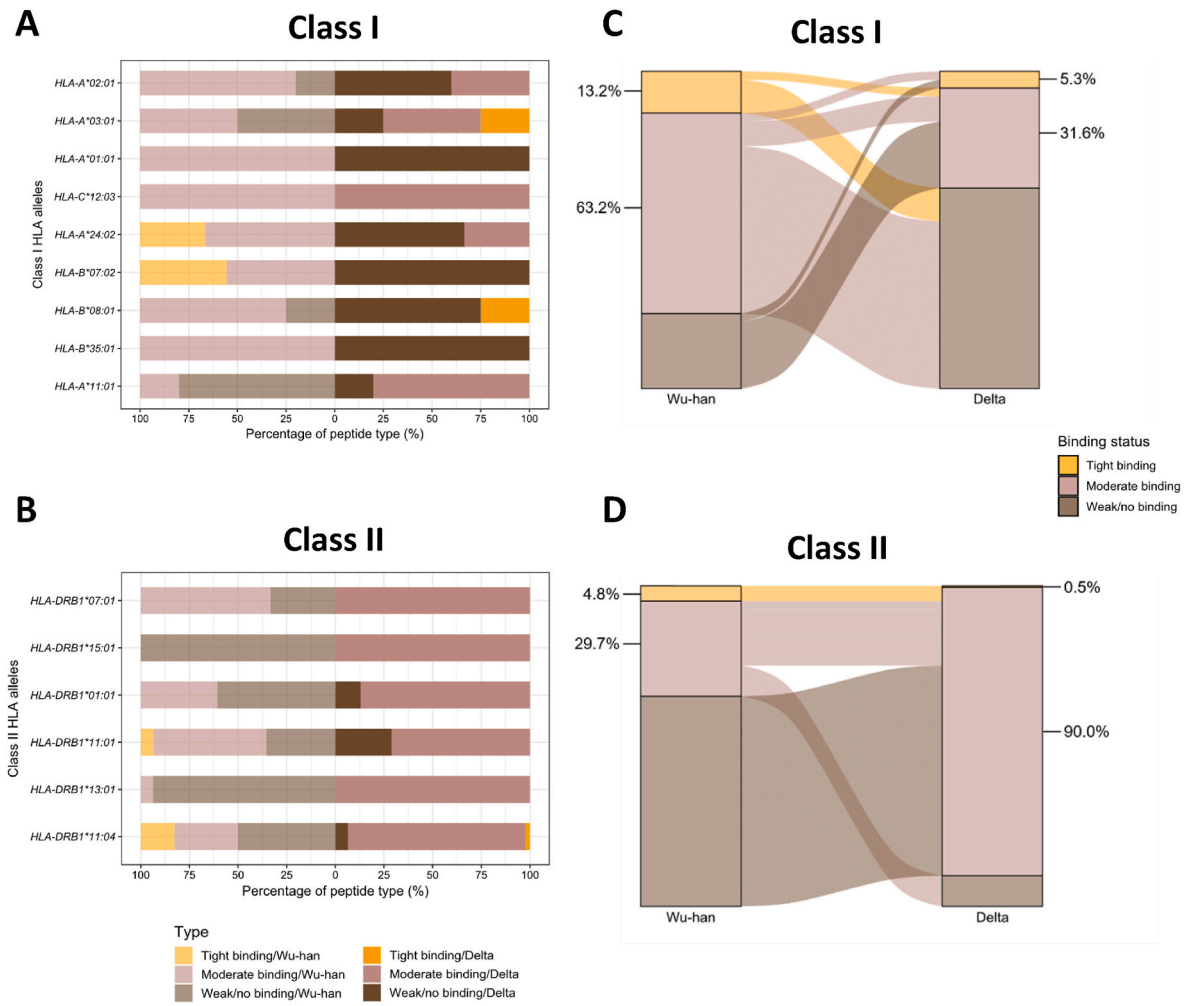

Fig. 4. Overview of binding affinity profiles changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Delta variant in the Russian population. (A, B) Detailed binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Delta variant in the Russian population, separately for (A) class I HLA alleles and (B) class II HLA alleles. (C, D) Overall binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Delta variant in the Russian population, separately for (C) class I HLA alleles and (D) class II HLA alleles.

4. Discussion

In general, the activation of T cells is initiated by the antigen presented at human leukocyte antigen (HLA), the variations of which, can influence the recognition of viral peptides by the immune system. As such, it is plausible that diverse disease susceptibility exists among individuals due to their variation of HLA alleles. Using the T-cell COVID-19 Atlas (T-CoV) database, we herein set the Wuhan strain as the reference to analyze the changes in the binding affinities of HLA molecules to the mutated SARS-CoV-2 peptides present in the Delta and Omicron variants, and compared the results between an Asian group and two European groups. For the altered peptides (compared to the Wuhan strain) in the Delta variant, we found a reduction of tight bindings in these three populations (Figs. 2, Fig. 3, Fig. 4). In the Taiwanese population, almost all the altered peptides with tight binding affinity in the Delta variant vanish. Regarding to the altered peptides in the Omicron variant, on the other hand, we found nearly equivalent proportion (~4%) of tight bindings to HLA class I and class II in the British population, and a larger proportion (~6.1%) to HLA class I than that to class II (~1.4%) in the Taiwanese population (Figs. 5 and 6). In comparison, the Russian population shows relatively high proportions of strong bindings to both HLA class I (~7.8%) and class II (~5.4%, Fig. 7).

In this study, we noticed that HLA-C *04:01 is predominant in the British and the Russian populations, yet relatively rare in the Taiwanese population. Nevertheless, minor change was found for the altered peptides with strong binding affinities presented by HLA-C *04:01 between the Wuhan and the Omicron strains. HLA-A*11:01, another class I allele, has been reported to associate with severe clinical outcomes of SARS-CoV-2 in the Japanese [21] and the Chinese populations [22]. Khor et al. used a high resolution sequencing-based HLA typing to explore the correlation of HLA alleles and haplotypes with the severity of SARS-CoV-2 infection in the Japanese population. A risk prediction model was thereafter proposed utilizing HLA-A*11:01, age at diagnosis, and sex at birth. Of note, HLA-A*11:01 was first identified as a risk allele for the severity of SARS-CoV-2 infection in the Chinese population [22]. Using deep sequencing to analyze 332 SARS-CoV-2 patients, Wang et al. also reported that HLA-A*11:01, B*51:01, and C*14:02 alleles are associated with the severity in SARS-CoV-2 infection. Examining these alleles in this study, we found that the frequencies of HLA-A*11:01 are higher than 5% in all the three populations, whereas HLA-B*51:01 and HLA-C*14:02 are at low frequencies and were thus excluded in our study. For the altered peptides with strong binding affinities to HLA-A*11:01, minor differences were found between the Wuhan and the Delta strains in the Taiwanese population, yet differences were observed between the Wuhan and the Omicron strains in the Taiwanese and the British populations. In addition, HLA class I alleles including

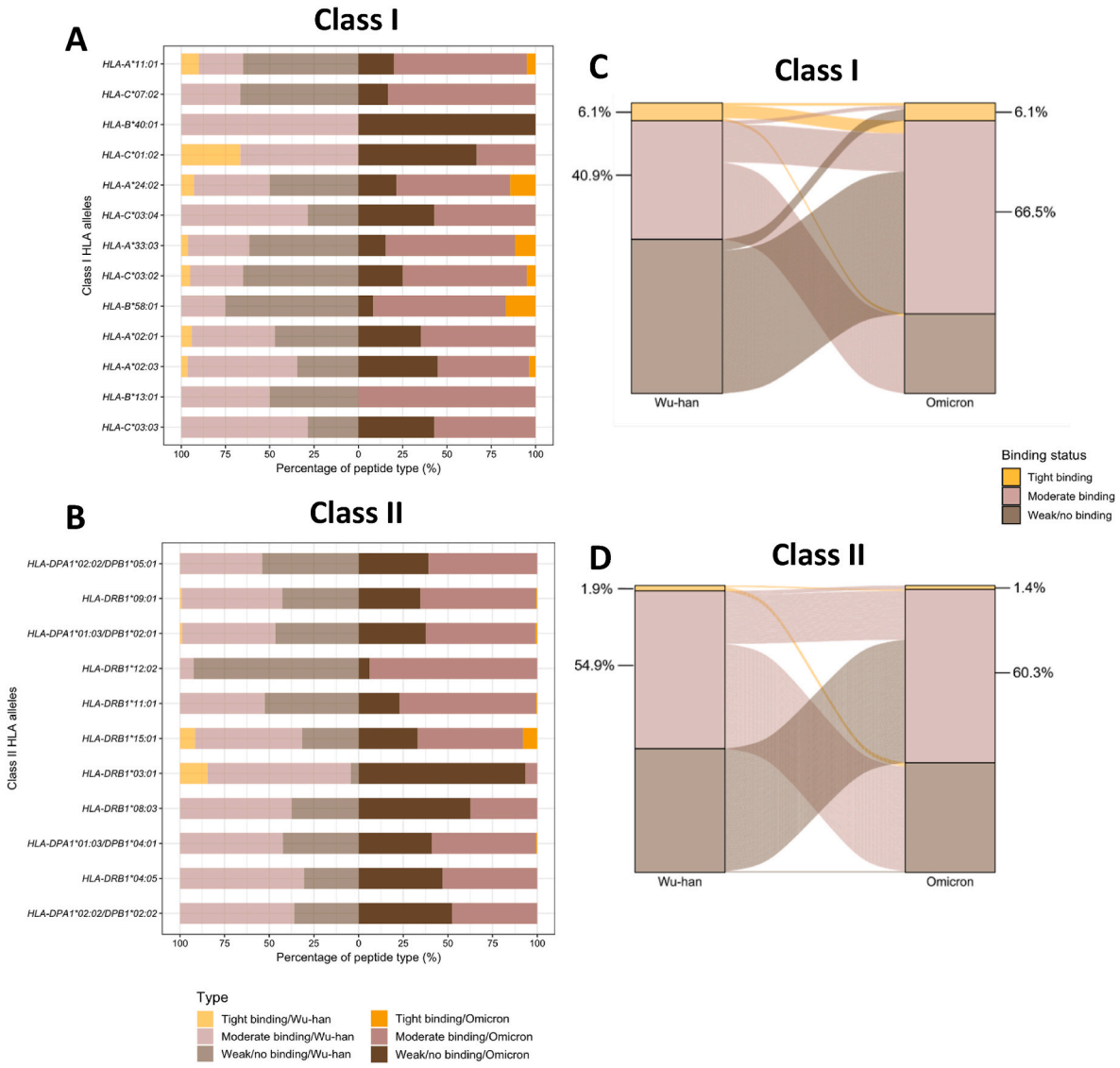

Fig. 5. Overview of binding affinity profiles changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Omicron variant in the Taiwanese population. (A, B) Detailed binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Omicron variant in the Taiwanese population, separately for (A) class I HLA alleles and (B) class II HLA alleles. (C, D) Overall binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Omicron variant in the Taiwanese population, separately for (C) class I HLA alleles and (D) class II HLA alleles.

HLA-B*46:01 and HLA-B*15:03 have been reported to associate with SARS-CoV-2 infection. For example, Nguyen et al., described a global HLA susceptibility map by investigating 48,395 unique peptides from SARS-CoV-2 proteome and mapped HLA-B*46:01 with the fewest predicted viral peptides, suggesting that HLA-B*46:01 is a high susceptibility allele for SARS-CoV-2 infection as it can barely recognize the virial peptides. By contrast, HLA-B*15:03 possesses the largest capacity of binding affinity to SARS-CoV-2 peptides, implying that it is a protective allele against SARS-CoV-2 infection [23]. However, the identification of HLA-B*46:01 as a risk allele was not replicated in study in the Japanese and the European populations [21]. Comparing the altered peptides with strong binding affinities of HLA-B*46:01 between the Wuhan and the Delta strains and between the Wuhan and the Omicron strains, we did not find any differences either. As for HLA-B*15:03, it was excluded in this study due to its low frequency.

Different from wet lab experiments, *in silico* prediction is an effective way to evaluate the alleles-associated peptides. Here, the binding affinities between the SARS-CoV-2 peptides and the HLA molecules were applied by netMHCpan-4.1 and netMHCIIpan-4.0 softwares. The strength of binding affinities therein is further classified into three categories: tight or strong binding (IC50 $<$ 50 nM), moderate binding (50 nM $\leq$ IC50 $<$ 500 nM), and weak or no binding (IC50 $\geq$ 500 nM). Although the findings can differ significantly among analysis strategies, a combination of *in silico* modeling and biological validation has seen success in investigating the peptides that bind to the allele-specific HLA molecule. For example, Sette et al. had performed a functional study to identify the correlations between the binding affinity of T-cell epitopes to HLA class I molecules and their immunogenicity. Their results showed that binding affinities of 50 nM or less are apparently immunogenic [24]. Such criterion (IC50 $<$ 50 nM) has further been applied to predict peptides with strong binding affinities to MHC class I and/or class II molecules in cancer immunotherapy and vaccine development [25–27]. Here, our analyses were primarily focused on the altered peptides with strong binding affinity from the Spike protein of SARS-CoV-2. We showed that the percentage of altered peptides with strong binding affinity (IC50 $<$ 50 nM) is generally reduced from the Wuhan to the Delta strain and from the Wuhan to the Omicron strain in all the three populations. These results suggest that the emergence of the Delta and the

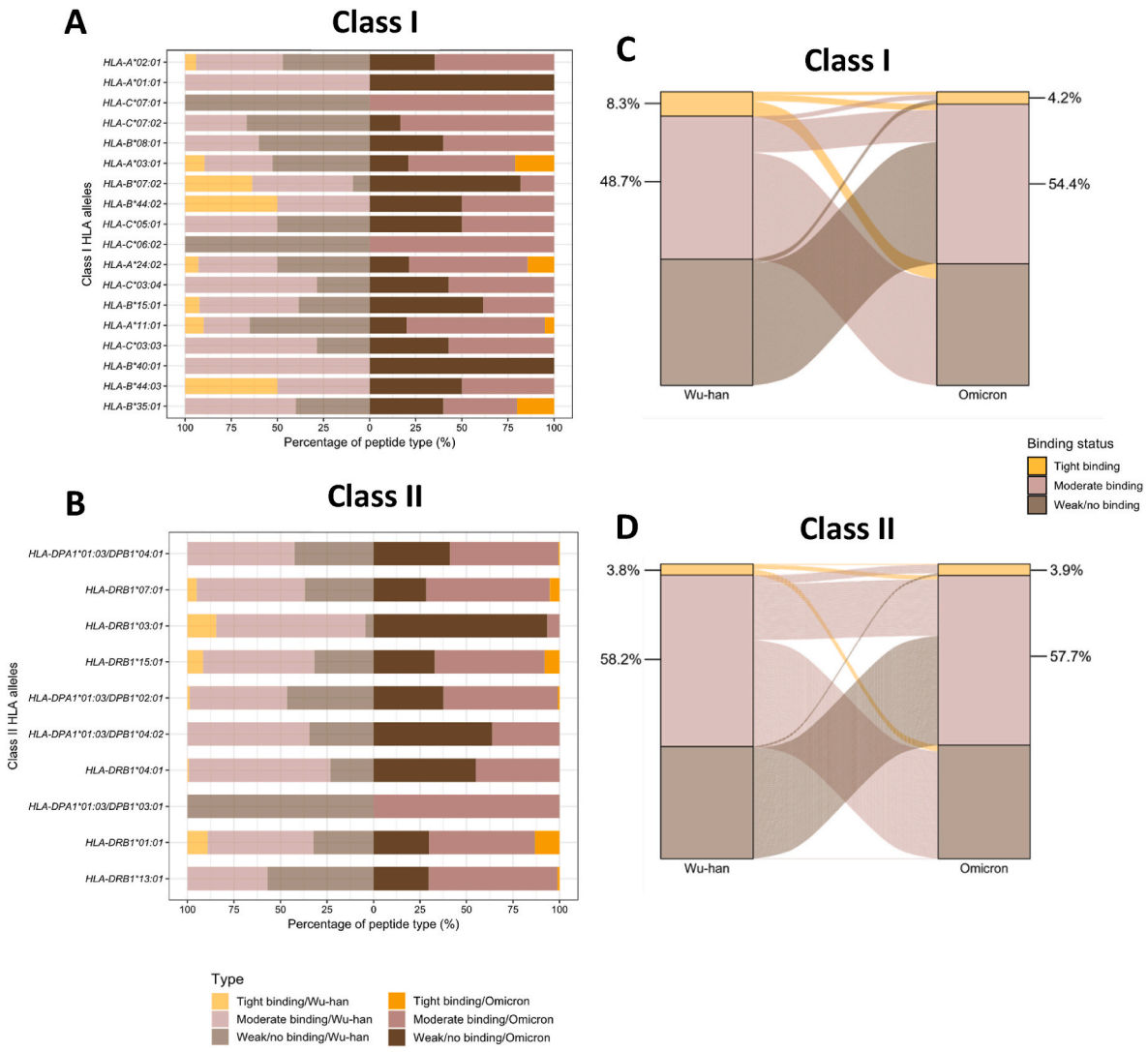

Fig. 6. Overview of binding affinity profiles changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Omicron variant in the British population. (A, B) Detailed binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Omicron variant in the British population, separately for (A) class I HLA alleles and (B) class II HLA alleles. (C, D) Overall binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Omicron variant in the British population, separately for (C) class I HLA alleles and (D) class II HLA alleles.

Omicron variants can bring challenges to the public health, as it currently stands. Moreover, as the current vaccines mainly target the Spike protein, selection pressures can occur to trigger the evolution of variants to evade immune recognition.

The changes in binding affinity of peptides to MHCs and T cell responses have been previously reported. Pfeiffer et al. demonstrated that a single amino acid alteration of immunogenic peptides enhanced the peptide binding to the MHC class II molecule, leading to the differentiation of CD4 T cells into Th1-like T cells [28]. Clancy-Thompson et al. showed that a neoantigen peptide with a higher binding affinity to the MHC class I molecule could promote a stronger cytokine production through the neoantigen-specific CD8 T cells [29]. These findings suggested that a stronger binding affinity of the altered peptide to the MHC class I/II molecules lead to enhanced CD8/CD4 T cell-mediated immune responses, both of which are important for the immunological protection against the viruses. Moreover, there is evidence demonstrating that mutations in SARS-CoV-2 cause an alteration of viral peptide presentation by MHC molecules. We have recently shown that co-localized mutations in the spike protein of the Omicron BA.1 (N211 deletion, L212I substitution and EPE 212–214 insertion) resulted in the dramatic loss of binding affinity with HLA-DRB1 *03:01 molecule, suggesting a mutation-induced immune escape of SARS-CoV-2 variants in T-cell recognition [30]. In line with such findings, Hamelin et al. reported that loss of T-cell epitopes binding for HLA-B7 types caused by alteration of peptides in SARS-CoV-2 variants [17]. Similarly, Xiao et al. found an impaired T-cell response to the Alpha variant (B.1.1.7) caused by mutations which disrupt peptide binding with HLA-A *02:01 [31].

There are certain limitations in our study. First, we mainly focused on the binding affinity profiles of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DPA1/DPB1. The role of HLA haplotypes was not investigated here. To analyze the altered binding affinity profiles more comprehensively, we considered that more access to the frequency of HLA-DQA1/DQB1 and other HLA haplotypes in three populations was essential. Second, all the binding affinity profiles were obtained from *in silico* prediction in T-CoV. Thus, experimental validations by pMHC tetramer [32] or pMHC multimer assay [33] will be helpful. Third, although the binding profiles of SARS-CoV-2 peptides to HLA molecules were evaluated, the recognition of peptide-HLA complexes by T-cell receptor (TCR) is not included. This recognition is important for a complete evaluation of the immune responses, as TCR diversity across individuals influences

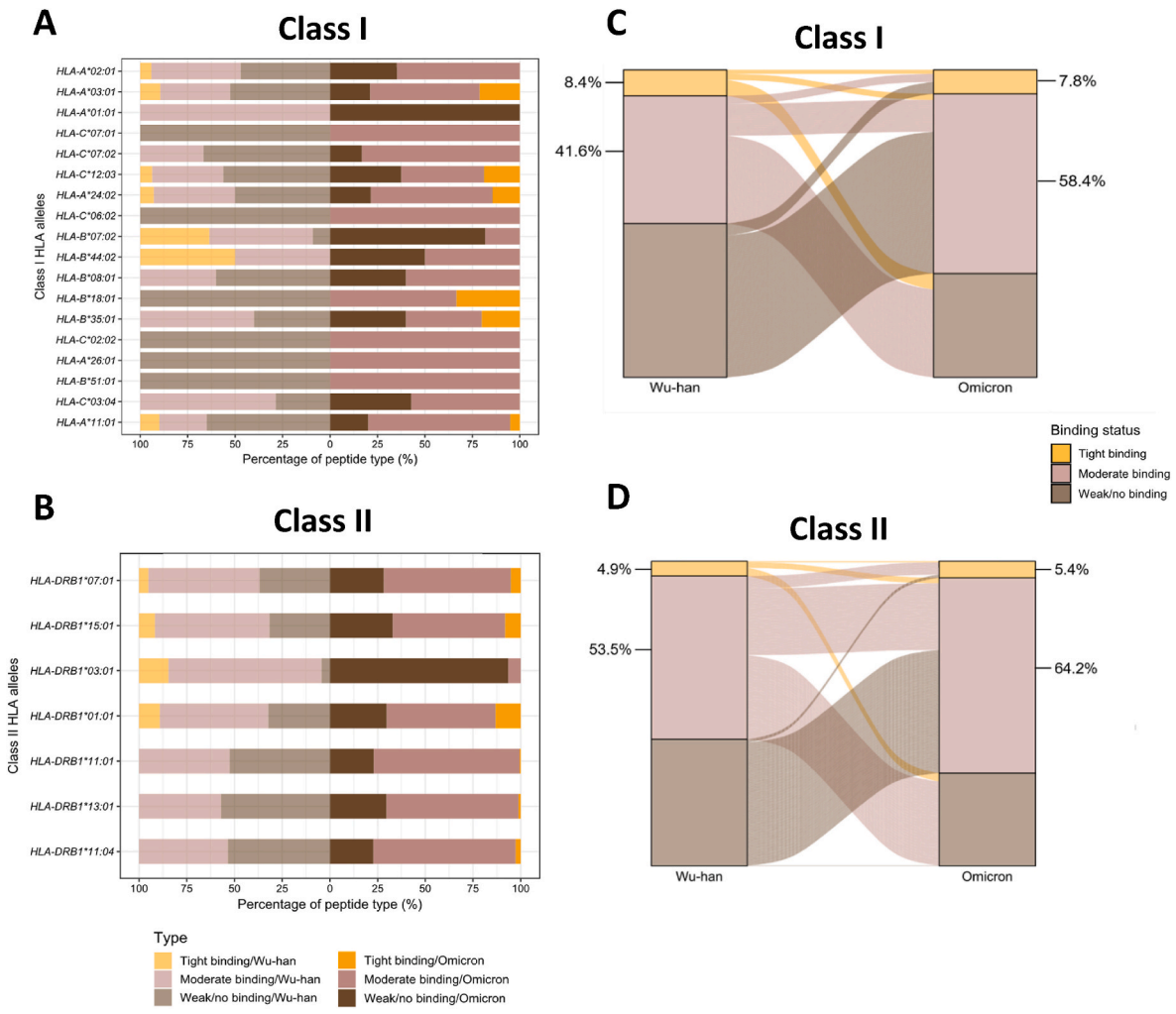

Fig. 7. Overview of binding affinity profiles changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Omicron variant in the Russian population. (A, B) Detailed binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Omicron variant in the Russian population, separately for (A) class I HLA alleles and (B) class II HLA alleles. (C, D) Overall binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Omicron variant in the Russian population, separately for (C) class I HLA alleles and (D) class II HLA alleles.

the immune response and clinical implications. Finally, the effectiveness of COVID-19 vaccines and policy implementation of city lockdown might cause the dynamic changes of transmission and clinical outcomes. Although we found the notable changes of HLA binding affinity to the Delta strain and to the Omicron strain among the three populations, no clinical evaluation was performed. We attribute this insufficiency to the variation of epidemic prevention policy and the complex factors in healthcare systems.

What might be the relevance of the HLA-peptides binding affinity profiles to the clinical findings? T cell-mediated antiviral responses are known to generate antibodies and trigger cytotoxic pathways for viral clearance. The loss of high-affinity peptides in the variants might weaken the immune response. Indeed, Charonis et al. found that the decline of vaccine effectiveness toward the mutated variants is associated with the decrease of high-affinity peptides to the HLA class II alleles [34]. Here, we comprehensively reported the changes in the HLA-associated SARS-CoV-2 peptide binding profiles among the Taiwanese, the British, and the Russian populations. Further studies are needed to understand the immunological mechanisms and the clinical values of our findings.

Author contributions

LCC, **WCC**, **CLG**, and **CJW** designed the study. **SN** and **AT** predicted the raw binding affinity data. All authors investigated the methodology. LCC and WCC wrote the draft manuscript. **LCC** and **CMC** analyzed the data. **LCC** and **CMC** visualized the data. **LCC**, **WCC**, **CLG**, **CMC**, CJW and **SN** interpreted the results. **WCC**, **LCC**, **CLG**, SN, and **CMC** wrote the revised article. CLG and WCC designed entire manuscript.

All authors reviewed and approved the final version of the article.

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Declaration of competing interest

Stepan Nersisyan is an employee of Armenian Bioinformatics

Institute (ABI). The authors declared no other conflict of interests in this work.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2022.102952.

The T-CoV database provided changes of binding affinity profiles between the Wuhan strain and the other variants for all proteins. To focus on the immune escape scenario for variants of concern nowadays, we extracted the altered binding peptides in the spike protein of two SARS-CoV-2 variants, the Delta variant and the Omicron variant in the database. On the other hand, we selected common HLA alleles (defined as allele frequency $\geq$0.05) in the Taiwan Biobank, the Oxford Biobank, and the Russian Federal Register of Bone Marrow Donors separately. With the population-specific common HLA allele profiles, we further selected the binding affinity profiles to altered spike peptides for three populations, the Taiwanese, the British and the Russian populations, to investigate population-specific SARS-CoV-2 variant spike peptide-common MHC binding landscape.

(A, B) Detailed binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Delta variant in the Taiwanese population, separately for (A) class I HLA alleles and (B) class II HLA alleles. (C, D) Overall binding affinities changed between the reference peptides in Wuhan strain and the corresponding altered (mutated) peptides in Delta variant in the Taiwanese population, separately for (C) class I HLA alleles and (D) class II HLA alleles.

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