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Comprehensive identification of high-frequency and co-occurring *Mafa-B*, *Mafa-DQB1*, and *Mafa-DRB* alleles in cynomolgus macaques of Vietnamese origin

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ABSTRACT

High-frequency alleles and/or co-occurring human leukocyte antigen (HLA) alleles across loci appear to be more important than individual alleles, because they might be markers of disease risk that have clinical value as biomarkers for targeted screening or the development of new therapies. To better elucidate the major histocompatibility complex background and to facilitate the experimental use of cynomolgus macaques, *Mafa-B*, *Mafa-DQB1*, and *Mafa-DRB* alleles were characterized and their combinations were investigated from 30 macaques of Vietnamese origin by cloning and sequencing. A total of 48 *Mafa-B*, 22 *Mafa-DQB1*, and 42 *Mafa-DRB* alleles, were detected in this study, respectively. In addition, two *Mafa-DQB1* and eight *Mafa-DRB* alleles represented novel sequences that had not been documented in earlier studies. Our results also showed that the macaque from Vietnam might be valuable because >30% of the test animals possessed *Mafa-DRB*w304* (30%) and *-DQB1*0616* (30%). We report that the combination of major histocompatibility complex (MHC) class I and II alleles, including the combination of *DRB3*0403-DRB*w304*, *DRB1*1013-DRB*w304,* and *Mafa-B*007:01:01-DRB*w304*, which was in 17%, 13%, and 13% of the animals, respectively. Interesting, more than two *Mafa-DQB1* alleles detected in one animal in this study suggest that *Mafa-DQB1*, like *Mafa-DRB*, might be a duplication in the chromosome, which have ever been documented in cynomolgus monkeys but has not yet been observed in rhesus macaques or other primates. Our results for the high frequency of commonly co-occurring MHC alleles across loci in a cohort of the Vietnamese cynomolgus macaque emphasized the value of this species as a model for biomedical research.

1. Introduction

With the 1978 ban on exportation of rhesus macaques (*Macaca mulatta*) from India, the cynomolgus macaque (*Macaca fascicularis*) became an increasingly useful animal model for various diseases, including diabetes, severe acute respiratory syndrome (SARS), tuberculosis, simian immunodeficiency virus (SIV), renal transplantation, and pharmacodynamic evaluation [1–4]. Major histocompatibility complex (MHC) class I and class II molecules play key roles in immune regulatory processes by presenting peptides of intracellular or extracellular origin to $CD8^+$ or $CD4^+$ T cells, respectively. It has been suggested that certain co-occurring alleles might be markers of disease risk that have clinical value as biomarkers for targeted screening or the development of new therapies [5]. A number of research groups have suggested that *HLA-DRB1/DQB1* and/or HLA classμalleles and haplotypes are associated with many diseases, including type 1 diabetes [6–10], pemphigus [11], pure red cell aplasia [12], allergies [13], low hepatitis activity [14], multiple sclerosis [15], primary Sjögren's syndrome [16], Graves' disease in Koreans [17], familial generalized vitiligo and early disease onset [18], lichen sclerosus [19], and rheumatoid arthritis [20,21]. It has been reported that the combination *B*4402-DRB1*1101-DQB1*0301* was associated with an 11-fold increased risk of cervical cell cancer [5].

For a few diseases, in particular SIV infection, macaques have become the dominant preclinical model for human immunodeficiency virus (HIV) vaccine evaluation [22,23]. There are many reports that show polymorphism of MHC genes in the cynomolgus macaque affects the results obtained with drugs [24–26] and is associated with the control of viral diseases [27]. The cynomolgus macaque from Mauritius appears to be particularly valuable, because 88% of these animals have the MHC class I allele combination *Mafa-A*25-A*29* [28] and more than half of these have the combination *Mafa-B*43010-B*44010-B*460101* [29]. The increased sharing of the MHC I allele in the Mauritian cynomolgus macaque might dramatically reduce the overall number of animals needed to study cellular immune responses in nonhuman primates and simultane-

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Table 1
Primers used to amplify *Mafa-B*, *Mafa-DRB*, and *-DQB1* alleles

Locus	Primer name	Primer sequence (5′ to 3′)	Temp (°C)	Product (bp)
Mafa-B	B-F	TGGCAGCTCTGACAGTGA	52	893
	B-R	CTGCCTGGATAGAAACCG		
Mafa -DRB	DRB1-F	TGGCAGCTCTGACAGTGA	52	450
	DRB1-R	CTGCCTGGATAGAAACCG		
Mafa -DQB1	DQB1-F	GAAGAAGGCTTTGCGGAT	55	420
	DQB1-R	GTCGCCGTTCCTAATAAG		

Temp, temperature.

ously reduce the confounding effects of genetic heterogeneity in HIV/AIDS research [28–31]. The high-frequency alleles might be high-priority targets for additional characterization of the immune function [32]. In addition, co-occurring MHC alleles across loci appear to be more important than individual alleles. So, to examine the combination of MHC class I and class II alleles in a cohort of the Vietnamese cynomolgus macaque, the transcribed Mafa class I and II genes were characterized and analyzed by sequencing the polymorphic exon 2 of *Mafa-DRB* and *Mafa-DQB1* genes and exons 2 and 3 of the *Mafa-B* gene.

2. Subjects and methods

2.1. Animals

Whole blood samples from 33 unrelated test animals (*M. fascicularis*), originally from Vietnam, were provided generously by South China Primates Research Central. Whole blood samples (3–5 ml) withdrawn from each monkey were collected into ethylenediaminetetraacetic acid (EDTA)-treated vacuum tubes. All of the monkeys were clinically normal with no known diseases.

2.2. RNA isolation, cDNA synthesis, and cloning of MHC class i and ii cDNAs

For all of the animals used in this study, RNA was isolated from peripheral blood (Blood RNA kit, Omega Bio-Tek, Guangzhou, China) and subjected to One-Step reverse transcription–polymerase chain reaction (RT-PCR), as recommended by the supplier (Takara). To identify and investigate the presence and expression of *Mafa-B*, *-DQB1* and *-DRB*, the first strand cDNA (1 μl) was amplified in a 25-μl reaction volume using coding region-specific forward and reverse primers to amplify *Mafa-DQB1* and *-DRB* alleles for exon 2 and *Mafa-B* for exons 2 and 3 (Table 1). In general, amplification was carried out for 3 minutes

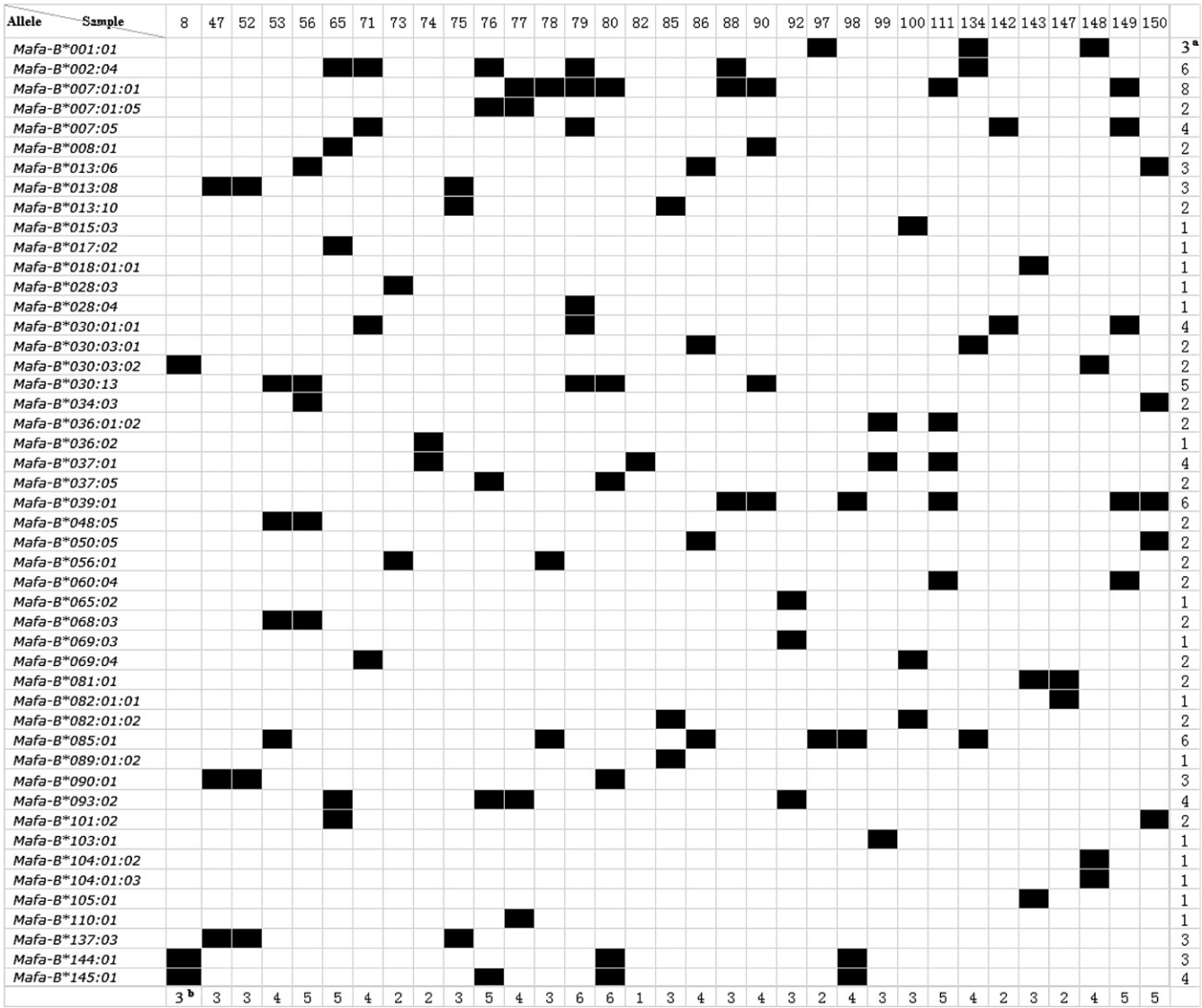

Fig. 1. Distribution of *Mafa-B* alleles detected in a cohort of Vietnamese cynomolgus macaques. [a]Number of animals sharing a certain allele. [b]Number of alleles in one animal.

at 94°C, 32 cycles of 30 seconds at 94°C, 30 seconds at 60°C, and 1 minute at 72°C, ending with 3 minutes at 72°C. The annealing temperature was adjusted based on the T_m of the primers. The PCR products were subjected to agarose gel electrophoresis and ethidium bromide staining for visualization and were cloned using the PCR cloning kit (Qiagen). After transformation, for each animal, 40 to 50 colonies per locus were picked for plasmid isolation and were bidirectionally sequenced by service provider (Invitrogen, China).

2.3. Data analysis and nomenclature

Using Mega 4.0 software [33], the sequences of the exon 2 regions of *Mafa-DRB*, *-DQB1*, and the exons 2 and 3 of *Mafa-B* obtained in our study were aligned. New alleles were confirmed by sequencing three times. The names of new sequences were derived according to the published guidelines, and the Immuno Polymorphism Database of Major Histocompatibility Complex for Non-human Primates (IPD-MHC NHP) was searched to avoid the same name(s) being assigned to different alleles [34,35].

3. Results and discussion

3.1. Identification and allele frequencies of transcribed Mafa-B, Mafa-DRB, and -DQB1 alleles

A total of 48 *Mafa-B* alleles were identified in this study by cloning and sequencing of exon 2 and 3 of the *Mafa-B* gene using whole blood from 33 randomly chosen test animals. Their accession numbers are listed in the supplementary data file (Table S1). From one to eight *Mafa-B* alleles ranging were identified in the 33 individual animals, and from two to five in 29 (88%) of the test animals. The most frequent allele was *Mafa-B*007:01:01*, which was found in eight (24%) of the 33 macaques. The second most frequent alleles were *Mafa-B*002:04*, *Mafa-B*039:01* and *Mafa-B*085:01*, all of which were detected in six (18%) individuals. The frequency of *Mafa-B*030:13* was 15% and the frequency was 12% each for *Mafa-B*007:05*, *Mafa-B*093:02*, *Mafa-B*037:01*, *Mafa-B*030:01:01* and *Mafa-B*145:01*. Another 15 alleles were present only once in these macaques (Fig. 2).

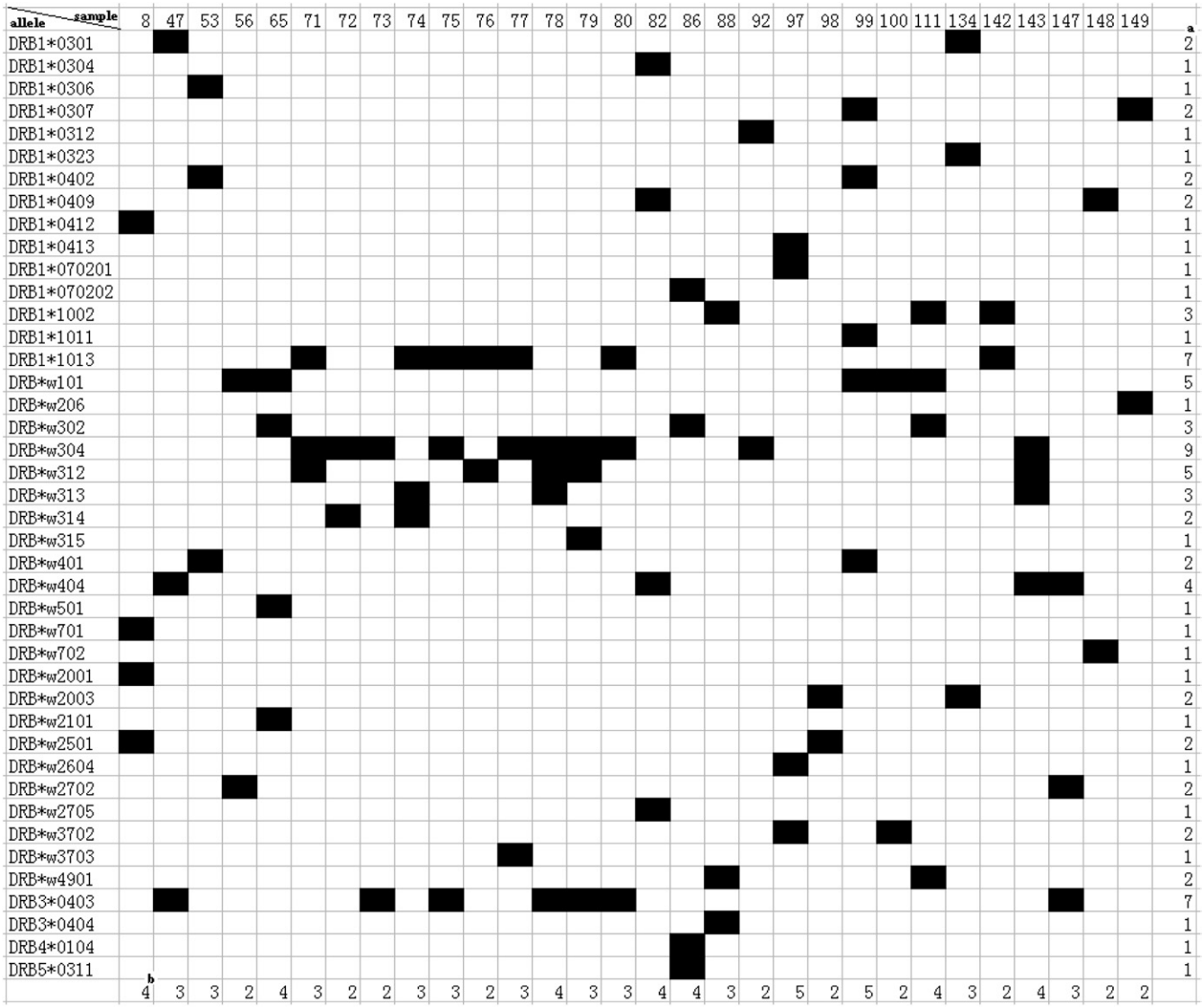

Fig. 2. Distribution of *Mafa-DRB* alleles detected in a cohort of Vietnamese cynomolgus macaques. [a]Number of animals sharing a certain allele. [b]Number of alleles in one animal.

It has been described that macaques from different origins have largely independent MHC I allele repertoires [29]. We found that some alleles including *Mafa-B*018:01:01*, *Mafa-B*036:01:02,* and *Mafa-B*037:01* were shared by these animals in the previous study [36]. Moreover, some alleles, including *Mafa-B*104:01:02* and *Mafa-B*104:01:03*, were highly similar to the *Mafa-B*104:01:01* allele that was detected in the Mauritian macaques [36]. Importantly, *Mafa-B*008:01* (HQ131700) and *Mafa-B*017:02* (HQ131701), which were identified in Vietnamese macaques in our previous study, are highly similar to *Mamu-B*08* and *Mamu-B*17*, respectively, which are associated with the control of viral replication in SIV-infected rhesus macaques. Surprisingly, we noted that one animal (macaque no. 65) expressed both *Mafa-B*008:01* and *Mafa-B*017:02* alleles, which were not expressed in the other macaques. However, these two populations might differ in their MHC class I allele repertoires [36]. The high-frequency MHC class I allele and its combination of *Mafa-B*430101*, *Mafa-B*440101,* and *Mafa-B*460101* from Mauritian cynomolgus macaques [29] has not been detected in our study.

In this study, 22 *Mafa-DQB1* alleles, two of which had not been reported in cynomolgus macaques, were identified by cloning and sequencing of exon 2 of the *Mafa-DQB1* genes using blood samples from 30 randomly chosen animals. These novel sequences were submitted to GenBank and were assigned accession numbers by the NHP Nomenclature Committee. Their accession numbers are listed in additional file (Fig. 1). All the new sequences are highlighted in italic and boldface type. All from one to two *Mafa-DQB1* alleles were expressed in individual animals but one animal in this study (Fig. 3). Interesting, three alleles were detected in this monkey (no. 76), suggesting that *Mafa-DQB1*, as well as *Mafa-DRB1*, is a duplication in the chromosome. As we know, it has been reported that more than two *Mafa-DQB1* alleles have been found in one animal [37]. Up to now, there have been no reports of the presence of duplicated *DQB* allele in other non-human primate or human but in cynomolgus macaques and cattle [37,38].

The most common sequences (40%) observed in this study belong to *DQB1*18* lineages (night alleles), the second most common (24%) belong to *DQB1*06* lineages (five alleles), the third most common belong to *DQB1*17* lineages (three alleles), and the rest belong to the *DQB1*15*, *DQB1*16,* and *DQB1*24* lineages. *Mafa-DQB1*0616* were the most frequently detected alleles in nine (30%) of the macaques, which was coincident with our previous study based on DNA level [39]. Moreover, 12 alleles were found only once (Fig. 3). It has been reported that most of the sequences (73%) observed belong to *DQB1*06* and *DQB1*18* lineages and the rest (27%) belong to *DQB1*15*, *DQB1*16,* and *DQB1*17* lineages in 105 randomly sampled Chinese rhesus macaques [40]. In addition, the *MhcMamu-DQB1*1706* allele, which corresponds to *MhcMafa-DQB1*170701* (100% similarity to *MhcMamu-DQB1*1706*) in the present study, was found in only three (2.86%) of 105 macaques in the previous study [39] and was also the low frequent (3.33%) in the 30 macaques tested in this study. Moreover, the *MhcMamu-DQB1*1503* allele found in animals infected with SHIV (a virus combining parts of the HIV and SIV genomes) with a lower plasma viral load was the second most frequent (19%) in 105 randomly sampled Chinese rhesus macaques [40], The *MhcMamu-DQB1*1503* allele, which corresponds to *MhcMafa-DQB1*1503* (100% similarity) in the present study, was the second most frequent (16.78%) in the 30 animals tested in this study. *Mafa-DQB1*1503*, one of the most frequent alleles in the present study, has been reported from different origins by many research groups, suggesting it is shared by cynomolgus macaques. The high frequency of the *Mafa-DQB1*0616* allele in the present study, which was also found in rhesus macaques from different origins [41], suggest it might be shared by cynomolgus macaque populations of different origins. However, neither has been detected in Mauritian cynomolgus macaques.

A total of 42 *Mafa-DRB* alleles, eight of which had not been reported in cynomolgus macaques, were identified by cloning and sequencing of exon 2 of the *MhcMafa-DRB* gene using blood samples from 30 randomly chosen cynomolgus macaques in this study. These novel sequences were submitted to GenBank and were assigned accession numbers by the NHP Nomenclature Committee. Their accession numbers are listed in additional file (Fig. 2). All the new sequences are highlighted in italic and boldface type. From 2 to 5 *Mafa-DRB* alleles were identified in individual animals. The allele with the highest frequency among these cynomolgus macaques was *Mafa-DRB1*w304*, which was found in nine (30%) of the 30 macaques. The next most frequent alleles were *Mafa-DRB1*1013*, which was a novel allele that was detected in seven (23.33%) of the macaques, and the frequency of both *Mafa-DRB1*w312* (a novel

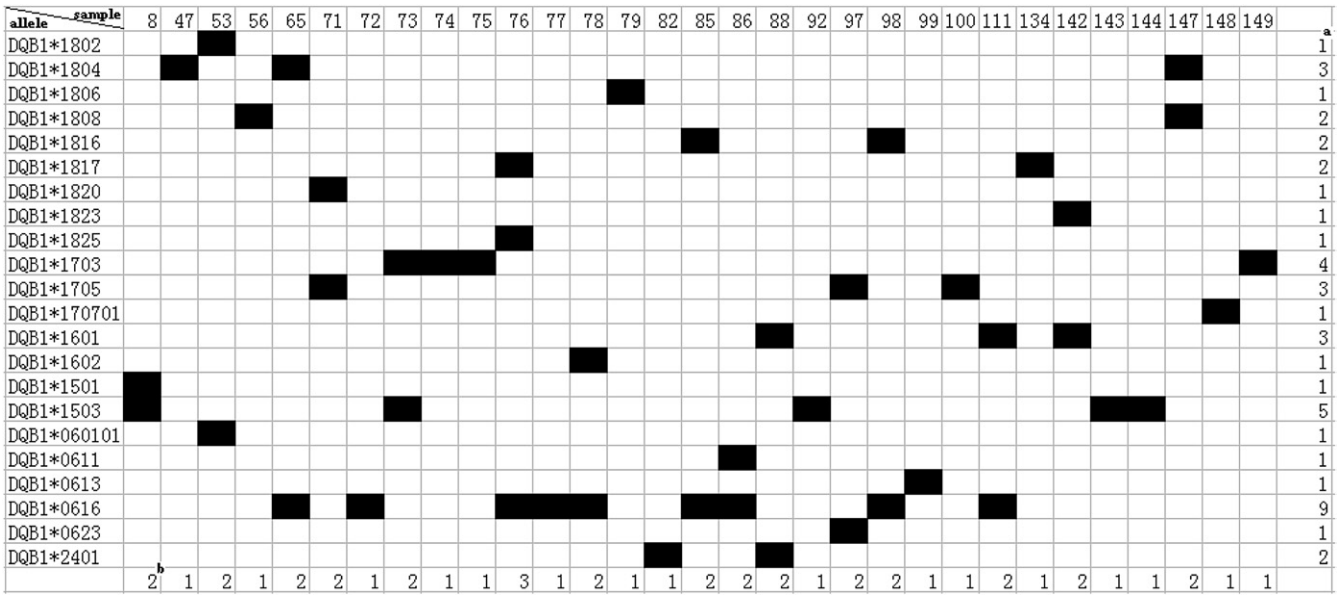

Fig. 3. Distribution of *Mafa-DQB1* alleles detected in a cohort of Vietnamese cynomolgus macaques. [a]Number of animals sharing a certain allele. [b]Number of alleles in one animal.

allele) and *Mafa-DRB1*w101* was 16.67% and 18 alleles were found only once in these cynomolgus macaques (Fig. 2). Alleles *MhcMafa-DRB3, MhcMafa-DRB4,* and *MhcMafa-DRB5*, as well as *MhcMafa-DRB*, were detected in this study. Among them, *Mafa-DRB3*0403* was highly frequent and was found in seven (23.33%) macaques.

*Mafa-DRB1*w304*, the most frequent allele in this study, has been reported in cynomolgus macaques that originate from islands not far from Borneo and Malaysia [37], but it has not been detected in Mauritian cynomolgus macaques [42]. The highly frequent *Mafa-DRB1*w101* allele in the present study had the second highest frequency in 40 Chinese cynomolgus macaques originating from the Guangxi Province in China [43]. However, the *Mafa-DRB1*0303* allele reported as the most frequent [43] was not identified in our study. We hypothesize that this difference is the result of the small number of animals in the present study.

3.2. Identification of co-occurring alleles Mafa-B, Mafa-DRB, and -DQB1

It has been suggested that co-occurring HLA alleles across loci appear to be more important than individual alleles, which are closely correlated with disease [5]. Mauritius cynomolgus macaques might be particularly valuable because more than half of these animals have the MHC class I allele combination *Mafa-B*430101*, *Mafa-B*440101,* and *Mafa-B*460101*. Recognizing that MHC molecules are codominantly expressed, we focused on co-occurring alleles. We investigated the combination of MHC alleles across loci in Vietnamese cynomolgus macaques. Our result showed that both *DRB3*0403* and *DRB*w304* alleles were detected in the five monkeys (nos. 73, 75, and 78 – 80), both *DRB1*1013* and *DRB*w304* were detected in the four monkeys (nos. 71, 75, 77, and 80), both *DRB*w304* and *B*007:01:01* were detected in the four monkeys (nos. 77-80), suggesting the combination of *DRB3*0403-DRB*w304*, *DRB1*1013-DRB*w304* and *DRB*w304-B*007:01:01* was in 17%, 13%, and 13% of the animals, respectively (Fig. 2). In addition, some combinations were in 10% of the animals, including *DRB1*1503-DRB*w304*, *DRB1*0616-DRB*w304*, *DRB1*0616-B*085:01,* and *DRB1*0616-B*007:01:01* (Fig. 4). Therefore, we conclude that extraordinary MHC class I and II allele sharing is a characteristic feature of Vietnam cynomolgus macaques.

It has been reported that 20% of animals have the *DRB*W2101-DRB*W501-DRB6*0101* haplotype [43], which is consistent with two earlier results demonstrating that more than 40% of macaques from Mauritius carried this haplotype [44,45]. Both *Mafa-DRB*W2101* and *Mafa-DRB*W501* alleles were found at low frequency (3%) in the Vietnam cynomolgus macaques bred at Guangdong Province in China; however, the *DRB6*0101* allele was not found in this study. It has been documented that MHC alleles/haplotypes were associated with sustained control of SIV-infected cynomolgus/rhesus macaques [22,23,30,31,46]. It has been shown that *Mamu-B*17*-positive SIV-infected rhesus macaques that also expressed these two MHC-II alleles had significantly lower viral loads than *Mamu-B*17*-positive animals that did not express *Mamu-DRB1*1003* or *-DRB1*0306* ($p < 0.0001$) [23]. The combination of *Mamu-DQB1*0601-DQB1*1801* and *Mamu-DQB1*0601-DRB1*0309-DRB*W201* alleles was found to be associated with rapid disease progression in SIV-infected rhesus macaques [22,46].

In conclusion, we suggest that Vietnamese cynomolgus macaques might be valuable because >30% of the test animals possessed *Mafa-DRB*w304* (30%) and *Mafa-DQB1*0616* (30%). The above high-frequency alleles among Vietnamese population may represent high-priority targets for additional characterization of immune function. Moreover, the combination of *DRB3*0403-*

Sample	DQB1*1503	DQB1*0616	DRB3*0403	DRB1*1013	DRB*W304	Mafa-B*007:01:01	Mafa-B*085:01
8	DQB1*1503						
47			DRB3*0403				
53							Mafa-B*085:01
56							
65		DQB1*0616					
71				DRB1*1013	DRB*W304		
72		DQB1*0616			DRB*W304		
73	DQB1*1503		DRB3*0403		DRB*W304		
74				DRB1*1013			
75			DRB3*0403	DRB1*1013	DRB*W304		
76		DQB1*0616		DRB1*1013			
77		DQB1*0616		DRB1*1013	DRB*W304	Mafa-B*007:01:01	
78		DQB1*0616	DRB3*0403		DRB*W304	Mafa-B*007:01:01	Mafa-B*085:01
79			DRB3*0403		DRB*W304	Mafa-B*007:01:01	
80			DRB3*0403	DRB1*1013	DRB*W304	Mafa-B*007:01:01	
85		DQB1*0616					
86		DQB1*0616					Mafa-B*085:01
88						Mafa-B*007:01:01	
90						Mafa-B*007:01:01	
92	DQB1*1503				DRB*W304		
97	DQB1*1503						
98		DQB1*0616					Mafa-B*085:01
99							
100							
111		DQB1*0616				Mafa-B*007:01:01	
134							Mafa-B*085:01
142				DRB1*1013			
143	DQB1*1503				DRB*W304		
147			DRB3*0403				
148							
149						Mafa-B*007:01:01	

The combination of *DRB1*1013-DRB*w304*
The combination of *DRB3*0403-DRB*w304*
The combination of *Mafa-B*007:01:01-DRB*w304*

Fig. 4. Distribution and combination of the most frequent alleles in a cohort of Vietnamese cynomolgus macaques. *Mafa-B/Mafa-DQB1/Mafa-DRB* combinations in this cohort of animals. *Mafa-B*, *Mafa-DQB1*, and *Mafa-DRB* cDNA sequences identified in three or more clones in each animal are shown. Only the highly frequent alleles of *Mafa-B*, *Mafa-DQB1*, and *Mafa-DRB* are listed.

*DRB*w304*, *DRB1*1013-DRB*w304,* and *DRB*w304-B*007:01:01* was in 17%, 13%, and 13% of the animals, respectively. In addition, more than two *Mafa-DQB1* alleles were found in one particular animal in the present study, suggesting that *Mafa-DQB1*, as well as *Mafa-DRB*, might be a duplication in the chromosome. This study is the first to reveal the high frequency of commonly co-occurring class I and class II MHC alleles across loci in a cohort of Vietnamese cynomolgus macaques, greatly enhancing the value of this species as a model for biomedical research.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.humimm.2012.02.003.

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