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A snapshot of the *Mamu-B* genes and their allelic repertoire in rhesus macaques of Chinese origin

Nel Otting · Corrine M. C. Heijmans ·
Marit van der Wiel · Natasja G. de Groot ·
Gaby G. M. Doxiadis · Ronald E. Bontrop

Abstract The major histocompatibility complex class I gene repertoire was investigated in a large panel of rhesus macaques of Chinese origin. As observed in Indian animals, subjects of Chinese derivation display *Mamu-B* gene copy number variation, and the sum of expressed genes varies among haplotypes. In addition, these genes display differential transcription levels. The majority of the *Mamu-B* alleles discovered during this investigation appear to be unique for the population studied. Only one particular *Mamu-B* haplotype is shared between Indian and Chinese animals, and it must have been present in the progenitor stock. Hence, the data highlight the fact that most allelic polymorphism, and most of the *Mamu-B* haplotypes themselves, are of relatively recent origin and were most likely generated after the separation of the Indian and Chinese rhesus macaque populations.

Introduction

The major histocompatibility complex (MHC) is a multi-gene family that plays a key role in initiating adaptive immune responses in vertebrates. Two main groups of genes and associated cell surface proteins are distinguished: class I molecules are involved in the binding and presentation of intracellular peptides, whereas class II gene products present processed extracellular antigen segments. An MHC class I or II molecule complexed with a peptide can interact with various types of receptors on distinct types of T and natural killer (NK) cells, which in turn may execute different kinds of effector functions. The main feature of the MHC is the abundant polymorphism of several of its genes, which may have a profound impact on disease susceptibility or resistance; it is also known to influence the outcome of organ transplantations. Moreover, the number of MHC class I and II genes may differ significantly between species (Kelley et al. 2005), as well as between individuals of a species (Robinson et al. 2003).

Due to its role in immune-related disorders, the MHC has been studied extensively, not only in humans (human leucocyte antigen (HLA) system) but also in non-human primates (Slierendregt et al. 1995; de Groot et al. 2002; O'Connor et al. 2003; Bontrop and Watkins 2005; Vierboom et al. 2005; Sauermann et al. 2008). In particular, the rhesus macaque (*Macaca mulatta*) is a commonly used animal model for the study of human diseases and vaccine development (Bontrop 2001). Orthologues of the HLA class I and II genes have been identified in rhesus monkeys and are named *Mamu-A*, *Mamu-B*, *Mamu-DP*, *Mamu-DQ* and *Mamu-DR* (Bontrop et al. 1995; Boyson et al. 1996; Doxiadis et al. 2001). Equivalents of non-classical class I genes, which are characterised by low levels of polymorphism and restricted tissue distributions, are also present in the rhesus macaque and are named *Mamu-E* and *Mamu-F* (Otting and Bontrop 1993; Boyson et al. 1995). In contrast to humans, the highly polymorphic classical class I *A* and *B* genes are multiplied in rhesus macaques (Daza-Vamenta et al. 2004; Kulski et al. 2004), whereas an equivalent of the

N. Otting (✉) · C. M. C. Heijmans · M. van der Wiel ·
N. G. de Groot · G. G. M. Doxiadis · R. E. Bontrop
Department of Comparative Genetics and Refinement,
Biomedical Primate Research Centre,
P.O. Box 3306, 2280 GH Rijswijk, The Netherlands
e-mail: otting@bprc.nl

HLA-C gene has not been observed (Vogel et al. 1999; Otting et al. 2005). Up until now, seven different *Mamu-A* genes, with differential transcription levels, have been defined. Combinations of two or three of these loci are present for every rhesus macaque chromosome that harbours the MHC region (Otting et al. 2007).

Orthologues of the *HLA-B* gene appear to have undergone several rounds of duplication in the rhesus macaque, as the sequence analysis of a complete rhesus macaque MHC region revealed a haplotype comprising 19 different *Mamu-B*-like genes (Daza-Vamenta et al. 2004; Kulski et al. 2004). Based on the promoter and exon sequences, it was concluded that 14 of these genes may have a protein-encoding capacity. Analyses of cDNA in pedigreed animals have shown, however, that only two or three loci per haplotype are transcribed at substantial levels (majors). In addition to these majors, minor alleles were also found, which are characterised by reduced transcription levels (Otting et al. 2005). Some minor *B*-like sequences appear to be alleles of an oligomorphic gene and may represent non-classical with a specialized function. An example is provided by *Mamu-I* (Urvater et al. 2000).

Most rhesus macaques used in research are of Indian origin, and most of the genetic data that have been gathered so far are based on animals from this subcontinent. In recent years, rhesus monkeys of Chinese origin have been introduced into the research, as well as cynomolgus (*Macaca fascicularis*) and pig-tailed macaques (*Macaca nemestrina*). cDNA analyses have suggested that these three species of macaque may share a similar organisation of the MHC class I A genes (Krebs et al. 2005; Pratt et al. 2006; Lafont et al. 2007; Otting et al. 2007). Phylogenetic comparison shows intermingling of the *Mamu-A*, *Mafa-A* and *Mane-A* alleles, which reflects the common ancestry of these species.

Considerable research has been performed on MHC class I B genes in the cynomolgus macaque, and about 80 *Mafa-B* alleles are known (Uda et al. 2005; Wiseman et al. 2007). Genomic sequencing of the MHC region in the cynomolgus macaque has revealed the presence of 12 *Mafa-B*-like genes on that particular haplotype (Watanabe et al. 2007). The investigation of Chinese rhesus macaques was started recently, and one report on 12 animals has documented the presence of 23 *Mamu-B* alleles (Karl et al. 2008). In the present study, an extensive panel of Chinese-origin animals was examined, with the aim of gathering more information on the makeup of the *Mamu-B* region. The lexicon of *Mamu-B* sequences has increased considerably, and with these sequences we intend to define the loci within the *Mamu-B* region, as has already been successfully performed for the *Mamu-A* and *Mafa-A* region (Otting et al. 2007). More information on distinct loci, and hence on configurations in the *Mamu-B* region, may help to establish

a more consistent nomenclature system for the *Mamu-B* alleles as well as for *B* alleles in other macaque species.

Materials and methods

Animals and cell lines

The Biomedical Primate Research Centre harbours a self-sustaining colony of approximately 1,000 rhesus macaques, mainly of Indian origin. The animals have been pedigreed based on the segregation of serologically defined MHC allotypes and other markers defined by molecular techniques (Doxiadis et al. 2003, 2006, 2007; Penedo et al. 2005). In recent years, the colony has been supplemented with individuals of Chinese origin, the pedigree status of which was unknown. A panel of 48 Chinese animals was selected for the present study. For most of these subjects, B-cell lines are available.

cDNA, cloning and sequencing

RNA was isolated from PBMCs or B cells (Rneasy kit, Qiagen) and subjected to One-Step reverse-transcriptase polymerase chain reaction (RT-PCR), as recommended by the supplier (Qiagen or Promega). The primers 5′MBS: AATT CATGGCGCCCCGAACCCTCCTCCTGC and 3′MBS: CTAGACCACACAAGACAGTTGTCTCAG were used that anneal specifically to *Mamu-B* transcripts in macaques. The final elongation step was extended to 30 min to generate a 3′ dA overhang. The RT-PCR products were cloned using the InsT/Aclone kit (Fermentas) or the PCR cloning kit (Qiagen). After transformation, 32 to 48 colonies were picked for plasmid isolation. Sequencing reactions were performed using the BigDye terminator cycle sequencing kit, and samples were run on an automated capillary sequencing system (Applied Biosystems Genetic Analyser 3100). The methods to determine high or low transcription levels have been published (Otting et al. 2005, 2007).

Phylogenetic analyses and nomenclature

Sequences were analysed using Sequence Navigator Software version 1.0.1 (Applied Biosystems) and MacVector™ version 9.5.2 (Oxford Molecular Group), followed by manual adjustments. Phylogenetic comparisons were also performed with the MacVector software. Neighbour-joining trees were constructed with the Kimura 2 parameter method, and bootstrap analyses were based on 1,000 replications.

Mamu-B alleles have been named according to published nomenclature proposals (Klein et al. 1990; Robinson et al. 2003; Ellis et al. 2006), and the alleles were submitted to the European Molecular Biology Laboratory database under accession numbers AM902528–AM902585.

Table 1 *Mamu-B* sequences observed in a panel of Chinese-origin rhesus macaques

Designation	Reference animals	Accession number
Majors		
***Mamu-B*010101**	Ri126, Ri165	U42837
*Mamu-B*010102*	Ri165	AM902529
***Mamu-B*0201**	Ri011	U41833
***Mamu-B*0301**	Ri037, Ri159	U41825
***Mamu-B*0401**	Ri037, Ri159	U41826
***Mamu-B*0702**	Ri165, Ri191	AJ556875
*Mamu-B*0704*	Ri011, Ri189	AM902528
*Mamu-B*1001*	Ri137, Ri185	AM902538
*Mamu-B*1301*	Ri011, Ri189	AM902539
*Mamu-B*1401*	Ri184, Ri233	AM902540
*Mamu-B*1501*	Ri079[a]	AM902541
*Mamu-B*1502*	Ri018	AM902542
*Mamu-B*1601*	Ri018	AM902543
*Mamu-B*1801*	Ri253[a]	AM902534
*Mamu-B*1903*	Ri126	AM902535
***Mamu-B*1902**	Ri028, Ri146	EF580169
*Mamu-B*2102*	Ri078	AM902536
*Mamu-B*2103*	Ri290[a]	AM902537
*Mamu-B*2301*	Ri284	AM902530
***Mamu-B*2401**	Ri028, Ri146	AJ556881
*Mamu-B*2501*	Ri289[a]	AM902531
*Mamu-B*280201*	Ri253[a]	AM902532
*Mamu-B*280202*	Ri290[a]	AM902544
*Mamu-B*2803*	Ri078	AM902545
***Mamu-B*3002**	Ri191	AJ844597
*Mamu-B*300302*	Ri281, Ri284	AM902546
*Mamu-B*300303*	Ri078	AM902547
*Mamu-B*3004*	Ri137, Ri142	AM902548
*Mamu-B*3201*	Ri289[a]	AM902549
*Mamu-B*3301*	Ri293	AM902550
*Mamu-B*3401*	Ri197	AM902551
*Mamu-B*3501*	Ri185	AM902552
***Mamu-B*3602**	Ri185	AJ556887
***Mamu-B*3701**	Ri185	AJ556888
***Mamu-B*3901**	Ri002, Ri026	AJ556890
***Mamu-B*4001**	Ri056	AJ556891
***Mamu-B*4002**	Ri018	EF362448/EF580150
*Mamu-B*4201*	Ri184	AM902553
*Mamu-B*440102*	Ri002	AM902555
*Mamu-B*4402*	Ri205	AM902556
*Mamu-B*4403*	Ri056, Ri189	AM902557
*Mamu-B*4404*	Ri302	AM902558
***Mamu-B*4502**	Ri185	AJ556896
***Mamu-B*4701**	Ri009	AJ556898
***Mamu-B*4702**	Ri136, Ri228	AJ556899
*Mamu-B*4703*	Ri090[a]	AM902560
*Mamu-B*4704*	Ri228, Ri260	AM902561
*Mamu-B*6102*	Ri078	AM902564
***Mamu-B*6601**	Ri197, Ri226	AJ844597
***Mamu-B*6701**	Ri009, Ri018	AJ844598
*Mamu-B*6702*	Ri028, Ri159	AM902568
***Mamu-B*680101**	Ri226, Ri233	AJ844599
*Mamu-B*680102*	Ri009, Ri018	AM902569
***Mamu-B*6802**	Ri018, Ri284	EF362453/EF219482

Table 1 (continued)

Designation	Reference animals	Accession number
***Mamu-B*6903**	Ri026	EF219479
*Mamu-B*6904*	Ri037	AM902574
***Mamu-B*7501**	Ri026	EF219478
***Mamu-B*7602**	Ri302	EF112569
*Mamu-B*7702*	Ri002, Ri184	AM902580
***Mamu-B*8301**	Ri281	EF580161
***Mamu-B*8501**	Ri094[a]	EF580165
*Mamu-B*8502*	Ri056, Ri189	AM902581
*Mamu-B*8602*	Ri287 ??	AM902582
*Mamu-B*8603*	Ri205	AM902583
***Mamu-B*8701**	Ri137, Ri142	EF580170
*Mamu-B*9102*	Ri009	AM902584
Minors		
***Mamu-B*0703**	Ri228	AJ556876
*Mamu-B*1703*	Ri165	AM902533
*Mamu-B*2702*	Ri228	AM902559
***Mamu-B*3801**	Ri009	AJ556889
*Mamu-B*5601*	Ri028, Ri159	AM902562
*Mamu-B*5901*	Ri233	AM902563
*Mamu-B*6201*	Ri094[a]	AM902565
***Mamu-B*6502**	Ri281	EF580163
*Mamu-B*6503*	Ri233	AM902567
*Mamu-B*6803*	Ri137, Ri142	AM902570
*Mamu-B*6804*	Ri253[a]	AM902571
*Mamu-B*7002*	Ri189, 226	AM902575
*Mamu-B*7201*	Ri182[a]	AM902576
*Mamu-B*7301*	Ri078	AM902578

Sequences in bold have been published previously. The names of some new alleles may have a lower lineage number than those already published because a series of vacant numbers was used for present designations. One or two reference animals are given for each allele.
[a] B-cell lines are not available

Results and discussion

Differential transcription levels: majors and minors

In the cohort of 48 Chinese rhesus macaques, 80 distinct *Mamu-B* sequences were detected, of which 51 have not yet been reported. The alleles are listed, together with the relevant accession numbers, as well as reference animals (Table 1). In most animals, three or four *Mamu-B* alleles were detected, which are considered to represent majors, as determined by the number of clones; this means that one to three majors may be present per haplotype. In most animals, additional *Mamu-B* sequences were found with low transcription levels, which represent minors (Table 1). Only those minor sequences were named and listed of which at least three identical clones had been detected. As a consequence, one should realise that the number of *Mamu-B* alleles detected in this study represents the tip of the iceberg since many minors may not have been picked up. Differential

transcription levels were earlier described for the *Mamu-B* alleles in Indian rhesus monkeys (Otting et al. 2005) and for genes in the *Mamu-A* and *Mafa-A* region (Otting et al. 2007). This phenomenon of varying transcription levels has been observed in other species as well (Birch et al. 2006; Wallny et al. 2006; Shaw et al. 2007).

In studies performed on Indian rhesus macaques, the peptide binding motifs of several *Mamu-A* and *Mamu-B* gene products have been defined (Evans et al. 1999; O'Connor et al. 2003; Sette et al. 2005; Kaizu et al. 2007; Loffredo et al. 2007). Comparisons indicated that the highly expressed *Mamu* class I molecules seem to execute the classical antigen presentation function, whereas the minors may represent non-classical genes. Alleles with a lower level of transcription are those of the oligomorphic *Mamu-I* locus (Urvater et al. 2000). *Mamu-I* has the characteristics of a non-classical and was probably once recruited by a duplication from one of the *Mamu-B* loci. The *Mamu-I* gene appears to be present on most haplotypes and will not be discussed in further detail.

Alleles that display the characteristics of a major in one animal and a minor in another have not been encountered. However, almost identical alleles were found that exhibit significant transcription differences. For instance, *Mamu-B*0702* is a major in some animals, whereas *Mamu-B*0703*, which differs by only one base pair, behaves as a minor (Table 1). The question arises as to how these differences in transcription took place. It is probable that the pool of paralogous *Mamu-B* genes has been generated by duplications (Kulski et al. 2004). Some of these paralogues may have acquired other unique mutations later, leading to distinct loci controlling unique lineages. A further level of complexity arose by unequal crossing over, which is often seen in multigene families. It is possible that during such processes apparently intact *Mamu* class I genes that belong to the same locus–lineage may have been placed in the context of promoters that render differential activity. Another possibility is that the genes and their promoters are tightly linked and that the promoter region itself was affected by mutations, leading to different transcription levels.

Sharing of *Mamu-B* alleles between populations

Phylogenetic analyses demonstrated that most of the alleles that are encountered in animals of Chinese or Indian origin share lineages. A phylogenetic tree, constructed of a selection of *Mamu-B* sequences (Fig. 1), illustrates, for instance, that members of the *Mamu-B*07*, *Mamu-B*19*, *Mamu-B*21* and *Mamu-B*68* lineages are present in both populations (*B*2001* should be renamed into a *B*68* allele). The difference between the alleles grouping within these lineage is explained by point mutations, although introns have not been sequenced to completely discard gene

conversion mechanisms. Crossing over events may be responsible for the generation of new lineages. It seems that after the physical separation of the Indian and Chinese rhesus macaque populations; these animals generated unique *Mamu-B* allelic repertoires. Indeed, in our Chinese panel, eight alleles were detected: namely, *Mamu-B*01*, *Mamu-B*0702*, *Mamu-B*2401*, *Mamu-B*3002*, *Mamu-B*3701*, *Mamu-B*3801*, *Mamu-B*4001* and *Mamu-B*4701*, which are present in Indian animals as well. However, three of these alleles are present on one haplotype and will be discussed in the next section. The sharing of alleles between populations seems to be independent of transcription levels. In the case of the *Mamu-A* locus, most of the alleles appeared to be population specific, and only one allele was shared between both groups (Otting et al. 2007; Karl et al. 2008). This would suggest that the *Mamu-A* alleles accumulate faster mutations than *Mamu-B*. This observation is in contrast to the situation encountered in humans and chimpanzees (Belich et al. 1992; Watkins et al. 1992; McAdam et al. 1994; McAdam et al. 1995; de Groot et al. 2000). It cannot be excluded that the population of Indian rhesus macaques has experienced a bottleneck (Hernandez et al. 2007). This phenomenon may explain the higher level of polymorphism within the population of Chinese rhesus monkeys.

Mamu-B haplotypes

In the Indian population studied previously, it was possible to determine the combination of *Mamu-B* alleles that segregate on a chromosome because pedigree data are available (Otting et al. 2005). The pedigree status of the presently studied Chinese animals is unknown. However, haplotypes can be deduced on the basis that particular *Mamu-B* allele combinations are observed in at least three animals. As can be seen, the deduced haplotypes are numbered subsequently and listed (Table 2). The most common Indian haplotypes are named and listed according to their corresponding serotype. Only one allele combination, represented by haplotypes 1 and B26, is common to both populations. This haplotype (*Mamu-B*01–B*0702–B*3002*) is of specific interest, as the B26 specificity in Indian animals seems to control resistance to develop collagen-type-II-induced arthritis (CIA) in young Indian rhesus macaques (Bakker et al. 1992). The peptide binding specificity of the *Mamu-B*01*

Fig. 1 Phylogenetic analysis of exons 2, 3 and 4 *Mamu-B* sequences obtained from Indian- and Chinese-origin rhesus macaques, as listed in Table 2. Indian-origin alleles are depicted in *yellow*; Chinese-origin alleles are shown in *blue*. The alleles depicted in *brown* are observed in both populations. The minor alleles have *mi* in their names. The locus numbers (in *black*) indicate the order in which transcribed alleles in haplotype B11a are present on the completely sequenced *Mamu-B* region (see also Table 3)
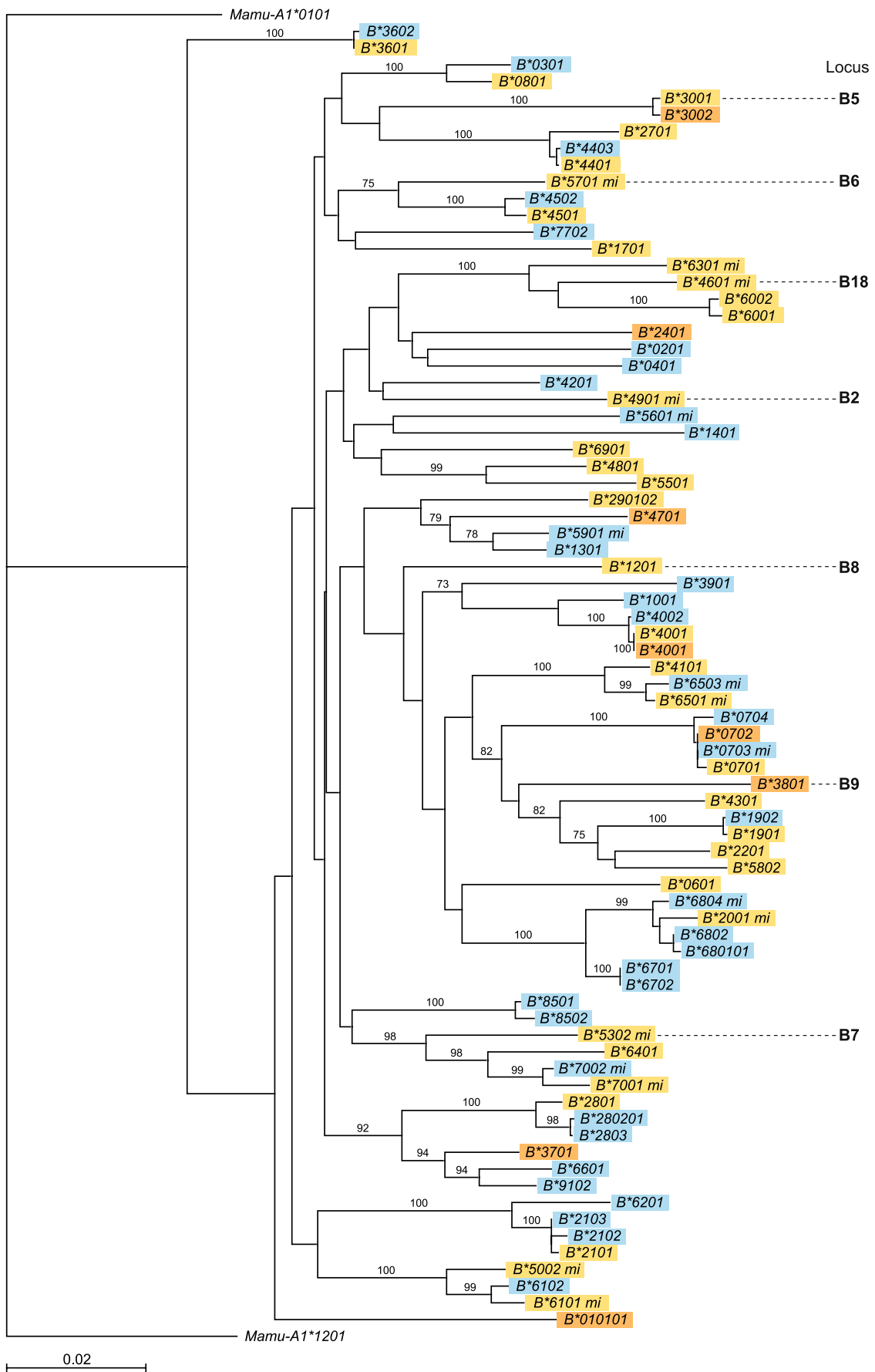
Table 2 Deduced combinations of alleles on chromosomes (haplotypes)

Haplotype	Majors	Minors
Chinese rhesus macaques		
1	B*010101/2, B*0702, B*3002	
2	B*1902, B*2401	
3	B*3602, B*3701, B*4502	
4	B*2102/3, B*2802/3, B*6102	B*6804 (B*20-like)
5	B*0301, B*0401	
6	B*6601, B*680101	
7	B*6701/2	B*5601
8	B*4403, B*8501/2	
9	B*4002, B*6802	
10	B*1001, B*6802	
11	B*0704, B*1301	B*7002
12	B*7702, B*4201	
13	B*1401	B*5901, B*6503
14	B*0201	
15	B*3901, B*0703	
Indian rhesus macaques		
B2	B*3801, B*4701	
B11a	B*1201, B*3001, B*3801	B*4601, B*4901, B*5302, B*5701
B11b	B*1201, B*3001, B*2201[a]	B*4601, B*4901, B*5302, B*5701, B*7001[a]
B13	B*4101, B*4801, B*6401	
B14	B*0601, B*0801	
B17	B*1701, B*290102, B*6002	B*6101
B18	B*5501, B*5802	B*6301
B20	B*2101, B*2801	B*2001 (B*68-like)
B24	B*1901, B*2401	
B25	B*6901	B*5002, B*6501
B26	B*010101, B*0701/2, B*3002	
B29	B*4001, B*4401	
B32	B*3601, B*3701, B*4501	

The Indian haplotypes are numbered according to associated serotypes. For the Chinese animals, reliable antisera are lacking, and the haplotypes are numbered successively. The B11a haplotype corresponds to the B region in the completely sequenced MHC.
[a] B*2201 and B*7001 sequences are not present on B11a.

gene product has been determined (Loffredo et al. 2005), so it will be of interest to assess whether Chinese animals, which express the Mamu-B*01 allotype, are resistant to the induction of CIA as well.

The Chinese haplotypes 2, 3 and 4 are the equivalents of the B24, B32 and B20 haplotypes encountered in Indian monkeys, apart from a few base pair differences in some alleles. Two Mamu-B allele combinations, 5 and 15, were encountered only twice in our panel but were confirmed by

other investigators (Boyson et al. 1996; Karl et al. 2008). A linked allele was not observed for Mamu-B*0201 (haplotype 14). In summary, the data show that in both macaque populations the number of majors transcribed per haplotype varies from one to three (Table 2). Although 14 functional Mamu-B-like loci may be present on the chromosome, only up to three loci are transcribed at considerable levels. Since an equivalent of HLA-C has never been found in the rhesus macaque, the overall number of classical class I gene products on the cell membrane in this animal seems to be comparable to the situation in humans.

Apart from the stable allele combinations, observed in both populations of macaques, majors are present that segregate with alleles from different lineages. The Mamu-B*6802 allele, for example, is found in combination with two majors: namely, Mamu-B*1001 and Mamu-B*4002, which are most likely different paralogous structures. Furthermore, the combination Mamu-B*4001–Mamu-B*4401 is frequent in Indian animals, whereas in Chinese animals members of the B*40 and B*44 lineages are not observed on the same chromosome (Table 2). The gene content of Mamu-B haplotypes may have been rearranged by recombination-like processes. The arrangement of the different Mamu-B genes is more prone to reshuffling than those of the Mamu-A region, which may be due in part to the high gene copy number variation in the Mamu-B region. This reshuffling of genes, in combination with the varying transcription levels, represents an alternative method for bearing polymorphisms within a population.

An attempt to define Mamu-B loci

One of the main consequences of the reshuffling of Mamu-B genes is the tremendous difficulty in assigning particular sequences to defined B genes or loci, as has been done for the Mamu-A and the Mafa-A regions. We have tried to

Table 3 Comparison of genomic sequences and cDNA transcripts for the Mamu-B11 region configuration

Locus–gene	Allele	Transcription level
Mamu-B2	Mamu-B*4901	Minor
Mamu-B3	Mamu-I	Minor
Mamu-B5	Mamu-B*3001	Major
Mamu-B6	Mamu-B*5701	Minor
Mamu-B7	Mamu-B*5302	Minor
Mamu-B8	Mamu-B*1201	Major
Mamu-B9	Mamu-B*3801	Major
Mamu-B18	Mamu-B*4601	Minor

In the first column, the Mamu-B loci as they appear on the completely sequenced rhesus MHC region are listed, in the next column which transcripts are observed as well as their transcriptions levels. For the other loci (B1, B4, etc.), no transcripts are detected with cDNA sequencing.

group *Mamu-B* alleles into loci by comparing them to the only published genomic rhesus macaque MHC region. The *Mamu-B* region published by Daza-Vamenta and co-workers matches our B11a serotype in Indian animals, and the major and minor alleles are listed in Table 3. Chinese and Indian animals share *Mamu-B* lineages, as is indicated by the intermingling of alleles in the phylogenetic tree (Fig. 1). The major and minor alleles of the B11 haplotype are indicated by a locus number that reflects their position on the sequenced B region. In the tree, clades are present that do not contain any of the loci present on the sequenced haplotype, for example, those with the *Mamu-B*21* and *Mamu-B*28* alleles. The phylogenetic analyses were also performed including the non-transcribed loci; however, clustering with *B*21* and *B*28* was again not observed (data not shown). Moreover, the sequenced haplotype appears to have a locus, represented by the major *Mamu-B*1201*, for which no orthologues are present in any other haplotype in our Chinese panel.

This observation underlines the fact that the number and combination of *Mamu-B* genes present per chromosome may differ dramatically between haplotypes, leading to various region configurations. At this stage, we do not understand whether any of the majors in different region configurations share paralogous or orthologous relationships. As discussed earlier, orthology or paralogy may be obscured by unequal crossing over events. Therefore, it is impossible at present to set up a nomenclature system for *Mamu-B* similar to that implemented for *Mamu-A* (Otting et al. 2007). Thus far, the *Mamu-B* alleles have been numbered mostly based on the order of detection. It is possible that the *Mamu-B* region is as plastic as the kinase inhibitory region in humans. Should this be the case, a nomenclature system for *B* alleles, which is based solely on lineage numbers, may provide a solution. However, a definitive choice with regards to nomenclature can only be made when additional data become available on the genomic organisation of more *Mamu-B* regions as well as on the *B* region of other macaques species.

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