Received: 28 February 2020 | Revised: 1 April 2020 | Accepted: 12 April 2020

DOI: 10.1111/iji.12490

REVIEW

INTERNATIONAL JOURNAL OF IMMUNOGENETICS WILEY

Comparative genetics of the major histocompatibility complex in humans and nonhuman primates

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Abstract

The major histocompatibility complex (MHC) is one of the most gene-dense regions of the mammalian genome. Multiple genes within the human MHC (HLA) show extensive polymorphism, and currently, more than 26,000 alleles divided over 39 different genes are known. Nonhuman primate (NHP) species are grouped into great and lesser apes and Old and New World monkeys, and their MHC is studied mostly because of their important role as animal models in preclinical research or in connection with conservation biology purposes. The evolutionary equivalents of many of the HLA genes are present in NHP species, and these genes may also show abundant levels of polymorphism. This review is intended to provide a comprehensive comparison relating to the organization and polymorphism of human and NHP MHC regions.

KEYWORDS

genetics, histocompatibility, immunology, molecular biology, nonhuman, polymorphism

1 | INTRODUCTION

The major histocompatibility complex (MHC) is a multigene family, and the proteins encoded by these genes play an important role in the adaptive immune response. The rise of the MHC correlates with the emergence of the jawed vertebrate species and dates back approximately 400 million years (Kasahara, Suzuki, & Pasquier, 2004). The MHC region is probably one of the most gene-dense regions in the mammalian genome, and many of its genes display abundant levels of polymorphism at the population level. In humans, the region is designated as human leucocyte antigen (HLA), and it is located on the short arm of chromosome 6 (band p21.3). Traditionally, the region is divided into three classes: MHC class I, II and III (Francke & Pellegrino, 1977). The MHC class I and II regions contain the genes encoding cell-surface molecules involved in the activation of the adaptive immune response as well as others essential in the antigen presentation pathway. The MHC class III region, situated between the class I and II regions, includes a variety of genes of which the gene products are involved in innate immunity or inflammation or in the regulation of immunity. In this review, the focus is on the MHC class I and II regions.

MHC class I molecules are composed of a heavy chain that is noncovalently bound to β_2-microglobulin (β_2M) and can be divided into a classical and a nonclassical group. The classical ones are expressed on virtually all nucleated cells. In humans, these molecules are designated as HLA-A, HLA-B and HLA-C. They function as peptide receptors that can signal, for example, infection. MHC class I molecules commonly present intracellularly processed peptides, approximately 9 amino acids in length (Falk, Rotzschke, Stevanovic, Jung, & Rammensee, 1991), to cytolytic $CD8^+$ T cells (CTL). Most of the time these are self-peptides, but if a foreign peptide is presented, this may result in activation of the CTL and subsequently the lysis of the infected cell. In addition, the classical MHC class I molecules act as ligands for killer cell immunoglobulin-like receptors (KIR) expressed on natural killer (NK) cells and a subset of T cells (Parham, Norman, Abi-Rached, & Guethlein, 2012;Trowsdale, 2001). The group of nonclassical MHC class I molecules, designated in humans as HLA-E, HLA-F and HLA-G, may show a restricted tissue distribution and a specialized function (Braud et al., 1998;Burian et al., 2016;Dulberger et al., 2017;Soderstrom, Corliss, Lanier, & Phillips, 1997). These molecules play a role in regulation of the NK cell response and can

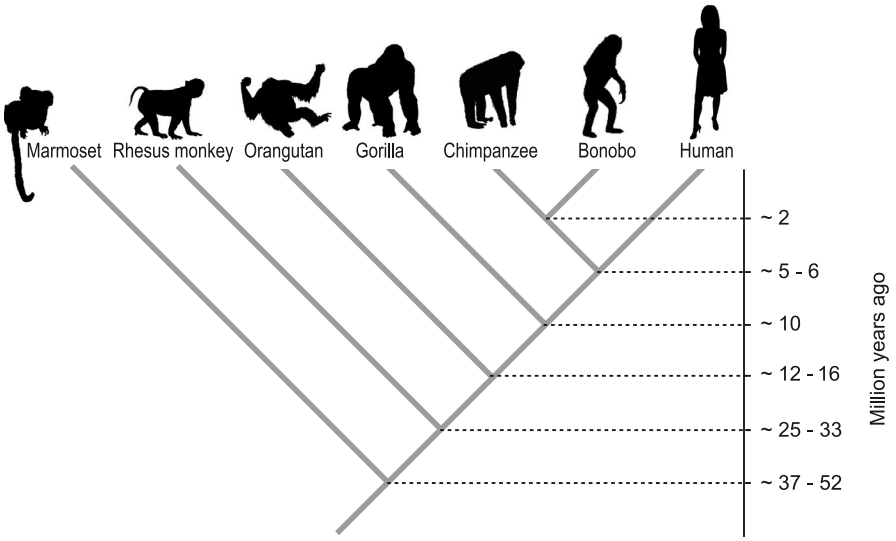


FIGURE 1 Evolutionary relationship of primate species. An estimation of the time frame relating to the most recent common ancestor is shown on the right-hand side of the figure

function as a ligand for CD49/NKG2 receptors and KIR receptors, or are a ligand for inhibitory leucocyte immunoglobulin-like receptors (LILRs) expressed on monocytes or subsets of T, B and NK cells (Braud et al., 1998;Dulberger et al., 2017;Shiroishi et al., 2003). Peptide loading of MHC class I molecules involves first the cleavage of the endogenous protein into peptides by the proteasome, followed by transfer of the peptides into the endoplasmatic reticulum (ER) by the transporters associated with antigen processing (TAP) molecules (Kelly et al., 1992;Kelly & Trowsdale, 2019). These transporter molecules map within the MHC region and are encoded as a heterodimer of the proteins TAP1 and TAP2 (Spies et al., 1990;Trowsdale et al., 1990). Subsequently, loading of the peptide on the MHC class I gene product takes place in the ER.

MHC class II molecules are heterodimers and are composed of an alpha (α) and a beta (β) chain, coded by the *A* and *B* genes. Three main types of MHC class II molecules are recognized in humans—designated DP, DQ and DR—which are predominantly expressed on professional antigen-presenting cells, such as dendritic cells, macrophages and B cells. They usually bind extracellularly derived peptides of approximately 13–25 amino acids in length and present them to $CD4^+$ T cells (Brown et al., 1988). MHC class II molecules regulate antibody responses and mediate $CD4^+$ T-cell help. The expression of MHC class II molecules on the cell surface can be induced or upregulated by interferon-gamma (IFN-γ), via the expression of the transcriptional activator MHC class II transactivator (CIITA) (Steimle, Siegrist, Mottet, Lisowska-Grospierre, & Mach, 1994). Furthermore, the MHC class II region is occupied by two genes encoding the MHC class II-like molecules DM and DO, which are involved in the peptide loading and transport of MHC class II molecules to the cell surface (van Ham et al., 1997). Briefly, MHC class II molecules associate with class II-associated invariant chain peptide (CLIP) in the ER. After localization to the small endosomes, the DM molecule can associate with the MHC class II molecule and facilitate CLIP removal. Peptide loading then takes place, and the MHC class II/peptide complex is transported to the cell surface (Denzin & Cresswell, 1995). The DO molecule, expressed mainly in B cells, is thought to interact with DM and has an inhibitory effect on the above-described reaction (Glazier et al., 2002;Leddon & Sant, 2010).

The MHC is most thoroughly studied in humans, mainly because of its importance in transplantation biology and its impact on health and disease. MHC research in nonhuman primates (NHP) is carried out because of the important role that several different NHP species may serve as preclinical models for human diseases such as AIDS, malaria, tuberculosis, multiple sclerosis and rheumatoid arthritis, but also in transplantation research (Fitch et al., 2019;Nakamura, Shirouzu, Nakata, Yoshimura, & Ushigome, 2019;t Hart, Bogers, Haanstra, Verreck, & Kocken, 2015;Watkins, Burton, Kallas, Moore, & Koff, 2008). In addition, the MHC in NHP receives increasingly more attention due to issues related to conservation biology (Arguello-Sanchez et al., 2018;Cao et al., 2015;Hans, Bergl, & Vigilant, 2017;Maibach, Hans, Hvilsom, Marques-Bonet, & Vigilant, 2017). True orthologues of the human MHC class I and II genes may be present in different NHP species. This review starts with a brief introduction on NHP, followed by an overview on the similarities and/or differences in the MHC class I and II regions in humans and various NHP species. In the final chapter, an overall summary is provided, and some additional examples are presented of how information on NHP MHC has contributed to our knowledge on the HLA system.

2 | HUMANS AND NONHUMAN PRIMATES

Approximately 150,000–200,000 years ago, the modern human lineage arose in Africa (Mellars, 2006), and from there, it began populating the different continents. Since then, the human population has greatly expanded, and it is estimated that there are more than 7.7 billion people living on our planet. From an evolutionary point of view, nonhuman primate species are humans' closest living relatives, and they are grouped into great and lesser apes, and Old and New World monkeys. The common chimpanzee (*Pan*

troglodytes, *Patr*) and bonobo (*Pan paniscus*, *Papa*) belong to the great ape species. Humans, chimpanzees and bonobos share a common ancestor that lived approximately 5–6 million years ago (Figure 1), and nearly 98.7% of their nonrepetitive DNA is similar (Fujiyama et al., 2002). The chimpanzee has its natural habitat in the forest and savannahs of equatorial Africa. Four subspecies are recognized; *P.t. verus*, *P.t. troglodytes*, *P.t. schweinfurthii* and *P.t. ellioti*. The bonobo inhabits different sections of forest lying south of the Congo River (Kawamoto et al., 2013;Zsurka et al., 2010). It is estimated that chimpanzees and bonobos shared a common ancestral species about 1.5–2 million years ago (Becquet, Patterson, Stone, Przeworski, & Reich, 2007;Prado-Martinez et al., 2013). The gorilla is the other African great ape species and lives in the tropical rainforests on that continent. There are two species—namely, the mountain (*Gorilla beringei*, *Gobe*) and the lowland (*Gorilla gorilla*, *Gogo*) gorilla—that shared with humans a common ancestor that lived roughly 10 million years ago (Figure 1) (Scally et al., 2012). Orangutans are the only contemporary great ape species living outside Africa, and they inhabit subsections of the Asian continent. The Sumatran and Bornean orangutan (*Pongo abelii*, *Poab* and *Pongo pygmeaus*, *Popy*, respectively) shared a common ancestor with humans approximately 12–16 million years ago (Figure 1) (Locke et al., 2011). Recently, a third orangutan species has been described (*Pongo tapanullensis*) that lives in the north of Sumatra (Nater et al., 2017). Lesser apes live also on the Asian continent, and their natural habitat includes the tropical and subtropical rainforest of different South-East Asian countries. Two types of lesser apes are distinguished—namely, the gibbon (*Bunopithecus*, *Hylobates* and *Nomascus* species) and the siamang (*Symphalangus* species)—that shared with humans a common ancestor that lived nearly 18 million years ago (Glazko & Nei, 2003;Perelman et al., 2011). Because at present little is known about the MHC of lesser apes, they will not be further discussed in this review.

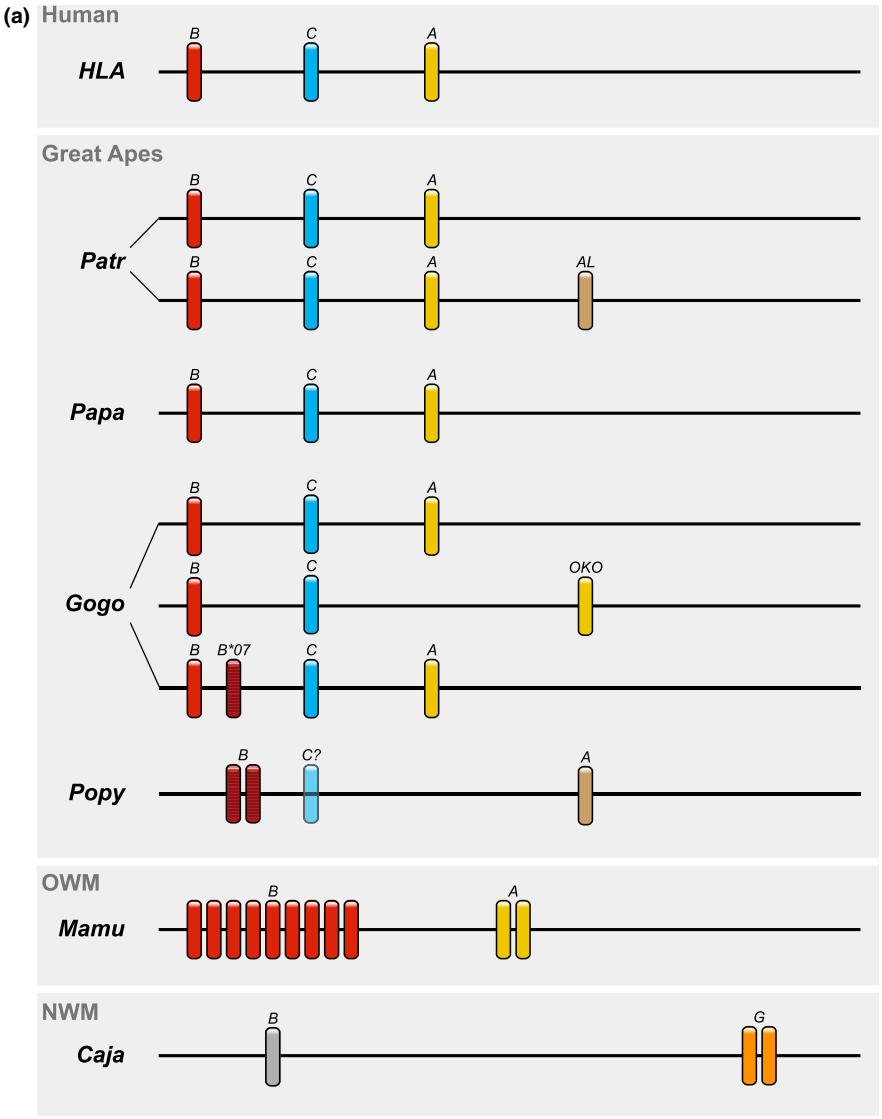
The Old World monkeys (OWM) and New World monkeys (NWM) represent two other large groups of NHP. The group of OWM consists of 24 genera and 138 species in total, which makes it the largest primate family (Groves, 2005). It includes different macaque and baboon species, which shared with humans a common ancestor that lived about 25–33 million years ago (Figure 1) (Glazko & Nei, 2003;Perelman et al., 2011). OWM are widespread and live in different environments in Africa and Asia. The Barbary macaque, however, is the only NHP that has a small section of Europe among its natural habitat, namely Gibraltar. The tropical regions of Central and South America as well as Mexico are the natural habitat of NWM species. Five different families have been defined: *Callitrichidae*, *Cebidae*, *Aotidae*, *Pitheciidae* and *Atelidae*. Well-known species are, for instance, the common marmoset (*Callithrix jacchus*) and cotton-top tamarin (*Saguinus oedipus*), the common squirrel monkey (*Saimiri sciureus*), night monkeys (*Aotus* species), saki monkeys (*Pithecia* species) and spider monkeys (*Ateles* species), respectively. The NWM group shared with humans a common ancestor about 37–52 million years ago (Figure 1) (Glazko & Nei, 2003;Perelman et al., 2011).

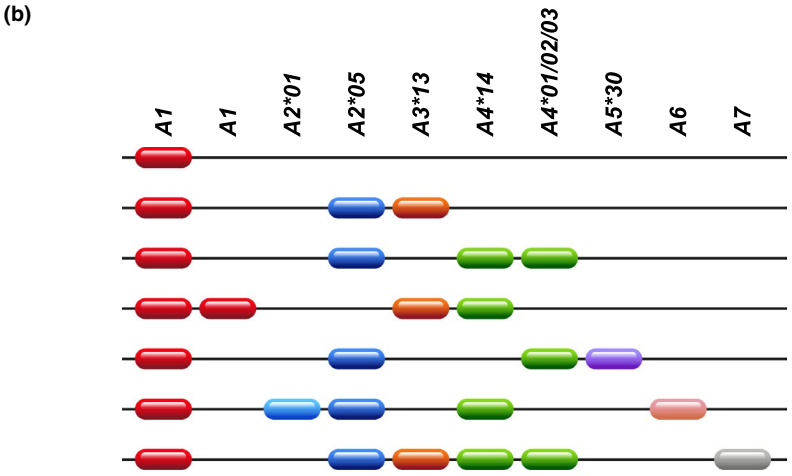
3 | MHC ORGANIZATION

3.1 | Organization of the classical MHC class I genes in primate species

In humans, the MHC class I region comprises one copy of the classical *HLA-A*, *HLA-B* and *HLA-C* genes per chromosome (haplotype). Established orthologues of these genes are present in chimpanzees and bonobos and are designated *Patr-A*, *Patr-B* and *Patr-C* and *Papa-A*, *Papa-B* and *Papa-C*, respectively (Figure 2a). Some chimpanzee MHC haplotypes may have an additional *HLA-A*-like gene, named *Patr-AL* (Adams, Cooper, & Parham, 2001;Geller et al., 2002). This gene, however, encodes molecules that have features resembling those of nonclassical HLA molecules (Goyos et al., 2015), and its evolutionary history seems to be complex (Maibach et al., 2017). In gorillas, the orthologues of *HLA-A*, *HLA-B* and *HLA-C* are also present and are named *Gogo-A*, *Gogo-B* and *Gogo-C* (Figure 2a). However, there are gorilla haplotypes that, instead of the *Gogo-A* gene, contain an *A*-related gene, designated *Gogo-Oko*, which is located at the same position as *Patr-AL* but shares characteristics with *HLA-A* (Hans et al., 2017;Lawlor, Warren, Taylor, & Parham, 1991;Watkins, Chen, Garber, Hughes, & Letvin, 1991). Furthermore, some gorilla haplotypes may have an additional copy of the *B* gene, named *Gogo-B*07*, which is more closely related to the orangutan *B* gene than to the *HLA-B*, *Patr-B* and *Papa-B* orthologues (Hans et al., 2017). Orangutan haplotypes contain one *Popy-A* gene (Figure 2a), and, although this gene is more closely related to *Patr-AL*, it appears to display significant levels of polymorphism (Adams et al., 2001;Gleimer et al., 2011). This finding suggests that the true orthologues of *HLA-A* are only present in the African great ape species. The *B* gene in orangutans shows copy number variation, and a minimum of two *B* genes per haplotype are observed (Chen et al., 1992;de Groot et al., 2016). In orangutans, a *C* gene is either present or absent (Adams, Thomson, & Parham, 1999;de Groot et al., 2016). The *C* gene arose from a duplication of a *B* gene in the progenitor species of humans and orangutans (Chen et al., 1992).

In OWM species, the apparent evolutionary equivalents of the *HLA-A* and *HLA-B* genes are present, but they lack the equivalent of *HLA-C* (Figure 2a). Macaques and baboons belong to the group of OWM and are most thoroughly studied for their MHC. Family studies and genomic data illustrated that the MHC class I region in OWM expanded massively during evolution and is far more complex than the *HLA* equivalent (Daza-Vamenta, Glusman, Rowen, Guthrie, & Geraghty, 2004;Doxiadis et al., 2013;Karl et al., 2013;Kulski, Anzai, Shiina, & Inoko, 2004;Otting et al., 2012;van der Wiel et al., 2018). In rhesus macaques (*Macaca mulatta*, *Mamu*), for example, a haplotype can contain one to two highly (major) and up to five low (minor) transcribed *A* genes (Doxiadis et al., 2013;Karl et al., 2013). To differentiate between the paralogous *A* genes, they are named *A1* to *A7* (de Groot et al., 2012, 2019). In cynomolgus macaques (*Macaca fascicularis*, *Mafa*), an *A8* gene can also be present (Shiina et al., 2015). In general, the *A1* gene displays the most polymorphism, whereas less polymorphism is observed for the *A2-A8* genes.


(a)
Human
HLA
B
C
A
Great Apes
Patr
AL
Papa
Gogo
OKO
B*07
Popy
C?
OWM
Mamu
NWM
Caja
G


(b)
A1
A1
A2*01
A2*05
A3*13
A4*14
A4*01/02/03
A5*30
A6
A7

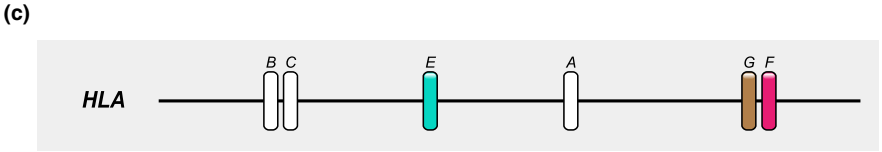

(c)
HLA
B C
E
A
G F

FIGURE 2 (a) Schematic organization of the MHC class I region in humans (HLA) and different nonhuman primate species (chimpanzee (*Patr*), bonobo (*Papa*), gorilla (*Gogo*), orangutan (*Popy*), rhesus macaque (*Mamu*) and common marmoset (*Caja*)). As compared to the organization in humans, chimpanzees may also have haplotypes that contain an extra *A*-like gene (*Patr-AL*) and that have features resembling that of nonclassical HLA molecules (Goyos et al., 2015); therefore, this gene is coloured in ochre in the figure. Some gorilla haplotypes include the *A*-related gene *Gogo-Oko*, which is located at the same position as *Patr-AL*, but shows characteristics of HLA-A (Hans et al., 2017;Lawlor et al., 1991;Watkins et al., 1991). In the figure, the gene is therefore indicated in the same yellow colour as HLA-A. For some gorilla haplotypes, an additional *B* gene (*Gogo-B*07*) is reported, indicated by the colour bordeaux in the figure, in order to highlight that it is more closely related to the orangutan *B* gene than to the *HLA-B*, *Patr-B* and *Papa-B* orthologues (Hans et al., 2017). The orangutan *A* gene is more closely related to *Patr-AL* and is therefore displayed in the figure in the corresponding colour. Furthermore, orangutan haplotypes have duplicated their *B* gene, and a *C* gene can be absent, which is indicated by a question mark. Rhesus macaque haplotypes comprise the evolutionary equivalents of the *HLA-A* and *HLA-B* genes, named *Mamu-A* and *Mamu-B*; therefore, these are indicated in corresponding colours. However, in contrast to *HLA-A* and *-B*, an expansion of the number of the *Mamu-A* and *Mamu-B* genes is observed. In common marmosets, the equivalent of the *HLA-B* gene, *Caja-B*, can be detected but it may be nonfunctional (Lugo & Cadavid, 2015); it is therefore presented in grey colour in the figure. The *Caja-G* gene is duplicated on a haplotype and encodes molecules that have taken over the classical antigen presentation function in common marmosets (Lugo & Cadavid, 2015;Watkins et al., 1990;van der Wiel et al., 2013). (b) Representative examples of *Mamu-A* haplotype configurations. The different paralogous *A* genes, *A1* to *A7*, which can be detected in rhesus macaques (*Macaca mulatta*, *Mamu*), are indicated at the top of the figure. For *Mamu-A2* and *Mamu-A4*, two different genes are described, designated *Mamu-A2*01* and *Mamu-A2*05*, and *Mamu-A4*14* and *-A4*01/02/03*, respectively, and they may be present on the same haplotype. To illustrate the diversity in haplotype configurations, each paralogous gene has been given its own specific colour. (c) Schematic organization of the nonclassical HLA class I genes, *HLA-E*, *HLA-F* and *HLA-G*. An identical organization can be found for these genes in great apes. In OWM and NWM species, the organization of the genes seems to be similar; however, species-specific expansion–contraction of the genes can be observed (Kono et al., 2014;Wu et al., 2018)

These latter genes are referred to as minors, because the products coded by these genes show lower levels of transcription and expression as compared to those of the *A1* gene (Rosner, Kruse, Lubke, & Walter, 2010;Wiseman et al., 2009). There is some evidence that the macaque *A2*05* gene performs a specialized function, as it is mainly found intracellularly, has a highly conserved antigen-binding site and primarily prefers 8-mer peptides as a ligand (de Groot, Heijmans, de Ru, et al., 2017). Currently, for the other paralogous *A* genes, the function is poorly understood. Figure 2b provides an overview of a few representative *Mamu-A* haplotype configurations, which is defined as the unique combination of different types of *A* genes on a chromosome (for a complete overview of macaque *A* haplotype configurations, see de Groot et al., 2019). The number of paralogous *Mamu-B* genes on a haplotype can reach up to nineteen, although most of these genes are not transcribed (Daza-Vamenta et al., 2004). A haplotype can comprise one to six major and one to ten minor transcribed *Mamu-B* genes (Daza-Vamenta et al., 2004;Doxiadis et al., 2013;Karl et al., 2013). Due to contraction and expansion of the rhesus macaque MHC class I region, haplotypes may carry a differential number of highly related *Mamu-B* genes, which makes it difficult at this stage to assign alleles to a particular *Mamu-B* gene or locus. Therefore, in contrast to *Mamu-A*, no locus numbers have been introduced as yet for most paralogous *Mamu-B* genes. Exceptions are *Mamu-I*, which was previously designated as *Mamu-B3*, and is an oligomorphic gene present on each haplotype (Urvater et al., 2000), and the pseudogenes *Mamu-B11*, *-B12*, *-B16* and *-B17*. Furthermore, macaque *B* transcripts may show differential expression across different leucocyte subsets, and this may have an effect on the MHC class I-restricted T-cell responses in macaque species (Greene et al., 2011).

Extensive research in different NWM species has failed to detect the evolutionary equivalents of *HLA-A* genes, suggesting that these are absent in NWM. The apparent equivalent of *HLA-B* can be detected in NWM and shows differential levels of expansion among different NWM species and a low level or tissue-specific expression in the family of *Callitrichidae* (e.g. common marmoset and cotton-top tamarin) (Lugo & Cadavid, 2015). Most NWM, however, display an expansion and diversification of the *HLA-G*-like gene (Figure 2a). In humans, HLA-G represents a nonclassical MHC class I molecule with features such as restricted tissue distribution and less polymorphism. The *HLA-G*-like gene in NWM has been found to encode molecules that seem to have taken over the classical MHC class I antigen presentation function (Lugo & Cadavid, 2015;Watkins et al., 1990;van der Wiel, Otting, de Groot, Doxiadis, & Bontrop, 2013).

In summary, particularly humans and great apes share a highly similar MHC class I region. Dissimilarities occur considering the number of MHC class I genes present on a haplotype (Figure 2a), which may vary significantly in different NHP species.

3.2 | Nonclassical MHC class I molecules

The equivalents of HLA-E, HLA-F and HLA-G are present in great ape, OWM and NWM species. The genes that encode these molecules display less polymorphism as compared to the genes encoding the classical MHC class I molecules and may often exhibit restricted tissue distribution. The gene encoding HLA-E is located on the centromeric side of *HLA-A* (Figure 2c). The genes encoding HLA-F and HLA-G are located on the telomeric side of *HLA-A*, in which the location of the gene for HLA-G is in closer proximity to *HLA-A* than the gene encoding HLA-*F* (Figure 2c). The IPD-IMGT/HLA database (https://www.ebi.ac.uk/ipd/imgt/hla/), a specialist database for sequences of the human MHC, comprises 84 *HLA-E*, 44 *HLA-F* and 69 *HLA-G* alleles, which encode 15 HLA-E, 6 HLA-F and 19 HLA-G proteins, respectively (numbers according release 3.39.0). In nonhuman primates, the nonclassical MHC class I genes are less thoroughly

investigated, and most studies have been based primarily on identification of the presence of the genes in a species. Table 1 provides an overview of the species in which the equivalents of *HLA-E*, *HLA-F* and *HLA-G* are documented, and for which data are available in the IPD-MHC NHP database (https://www.ebi.ac.uk/ipd/mhc/group/NHP), a specialist database for sequences of the MHC of NHP. In NHP, a similar organization has been found as described for *HLA-E*, *HLA-F* and *HLA-G* genes.

MHC-E binds and presents 9-mer peptides derived from the leader sequences of the classical MHC class I polypeptides to inhibitory CD94:NKG2A/B and activating CD94:NKG2C receptors to regulate NK cell activity (Braud et al., 1998;Braud, Jones, & McMichael, 1997). In addition, pathogen-derived peptides can be bound by MHC-E and successfully presented to MHC-E-restricted $CD8^+$ T cells (Joosten et al., 2010;Pietra et al., 2003;Salerno-Goncalves, Fernandez-Vina, Lewinsohn, & Sztein, 2004). In humans and nonhuman primate species, limited diversity is observed for *MHC-E*, and almost all primate species show a complete conservation of the peptide-binding groove of the corresponding molecule (Boyson et al., 1995;Knapp, Cadavid, & Watkins, 1998). For NHP, *MHC-E* polymorphism is most thoroughly investigated in the rhesus and cynomolgus macaque, and 33 and 16 different alleles are described encoding 30 and 14 proteins, respectively (Table 1). Rhesus and cynomolgus macaques may express 1–4 and 1–3 distinct MHC-E transcripts, respectively, suggesting that the *MHC-E* gene is duplicated in these species (Wu et al., 2018). Although the implications of this duplication in macaques are unclear, the HLA-E and the macaque counterparts show conservation concerning their T-cell immunity, which includes similar upregulation by viral pathogens and the presentation of identical viral peptides to $CD8^+$ T cells (Wu et al., 2018).

Only recently, a couple of studies shed some light on the functional properties of HLA-*F* (Burian et al., 2016;Burrows et al., 2016;Dulberger et al., 2017;Garcia-Beltran et al., 2016), which illustrated that it may exist as open conformers: the HLA-F heavy chain without β_2M and a peptide. In addition, the replacement of

TABLE 1 Different great ape, OWM and NWM species in which the equivalents of *HLA-E*, *HLA-F* and *HLA-G* are described

Scientific name	Common name	*MHC-E*	*MHC-F*	*MHC-G/-AG*
Gorilla gorilla	Gorilla	2 (1)	3 (3)	1
Pan paniscus	Bonobo			1
Pan troglodytus	Chimpanzee	2 (1)	6 (3)	1
Pongo pygmaeus	Bornean orangutan	1	1	
Pongo abelli	Sumatran orangutan		2 (1)	
Cercocebus atys	Sooty mangabey	3 (3)	4 (4)	
Chlorocebus aethiops	Grivet			2 (2)/ -
Chlorocebus sabaeus	Green monkey	3 (2)		-/ 1
Macaca fascicularis	Cynomolgus macaque	16 (13)	33 (22)	10 (9)/ 36 (27)
Macaca mulatta	Rhesus macaque	33 (30)	24 (18)	4 (4)/ 9 (8)
Macaca nemestrina	S. Pigtailed macaque	8 (8)	11 (7)	-/ 1
Papio anubis	Olive baboon		4 (3)	-/ 5 (4)
Papio cynocephalus	Yellow baboon	1		
Aotus lemurinus	Gray-bellied Night m.		5 (5)	
Aotus trivigatus	Three-striped Night m.	1		3 (3)
Ateles belzebuth	White-fronted spider m.	1		3 (3)
Ateles fusciceps	Black-headed spider m.	2 (2)		9 (9)
Callithrix jacchus	Common marmoset	3 (2)	11 (6)	108 (99)
Leontopithecus rosalia	Golden lion tamarin			2 (2)
Pithecia pithecia	White-faced saki	1		4 (4)
Saguinus fuscicollis	Brown-mantled tamarin			4 (4)
Saguinus labiatus	White-lipped tamarin			13 (8)
Sagiunus oedipus	Cotton-top tamarin	1	4 (4)	19 (11)
Saimiri sciureus	Common squirrel m.			1

Note: Shown is the number of alleles and, in brackets, the number of proteins that are encoded (m. means monkey; S. means Southern) (numbers are according IPD-release 3.4.0.0). The number of animals studied may vary from 1 to approximately 150, depending on the species and gene.

arginine (R) to tryptophan (W) at amino acid position 62 (R62W) of the HLA-F gene product converts HLA-F from an open conformer into a peptide-presenting molecule that associates with β_2M (Dulberger et al., 2017). This substitution is only observed in humans and orangutans, which most likely evolved independently in these two species, thus suggesting that in other primate species MHC-F molecules only appear as open conformers (Dulberger et al., 2017). HLA-F open conformers function as a ligand for NK cell receptors: for example, KIR3DS1 (Garcia-Beltran et al., 2016). The peptide-bound form of HLA-F has been shown to interact with leucocyte immunoglobulin-like receptor 1 (LIR1), also denoted in the literature as LILRB1 or Ig-like transcript 2 (ILT2) (Dulberger et al., 2017). Interaction with ILT4 (also denoted as LIR2 or LILRB2) is also described (Lepin et al., 2000). HLA-F can present peptides that vary in length and may be more than 30 amino acids long, and resembles the peptide binding as observed for MHC class II molecules (Dulberger et al., 2017).

HLA-G is expressed in the placenta by extravillous trophoblast cells, the foetal tissue that invades the uterine wall during embryo implantation at the beginning of pregnancy when the placenta is formed. The MHC-G in great apes shows a similar tissue distribution as well as limited polymorphism. In OWM, the equivalent of *HLA-G* is inactivated and became a pseudogene, and the function and exclusive tissue distribution have been taken over by the gene designated *MHC-AG* (Boyson, Iwanaga, Golos, & Watkins, 1997). *MHC-AG* is identified in several OWM species, and a limited amount of polymorphism is recorded in rhesus and cynomolgus macaques (Table 1). In NWM, as mentioned in the previous section, the apparent orthologue of *HLA-G* is present; however, in at least some of the NWM species, the *HLA-G*-like gene seems to fulfil the classical antigen presentation function (van der Wiel et al., 2013). The common marmoset is the most intensively studied NWM species, and 108 different *Caja-G* alleles distributed over 19 lineages are currently retrievable in the IPD-MHC NHP database. HLA-G acts primarily as ligand for the LILRB1 and LILRB2 receptors that are expressed on monocytes or subsets of T, B and NK cells (Shiroishi et al., 2003). Furthermore, the NK cell receptor KIR2DL4 may interact with HLA-G (Yan & Fan, 2005). Equivalents of the LILRB and KIR2DL4 receptor molecules are present in different nonhuman primates (Abi-Rached, Moesta, Rajalingam, Guethlein, & Parham, 2010;Blokhuis, van der Wiel, Doxiadis, & Bontrop, 2009;Canavez et al., 2001;Guethlein et al., 2017;Prall et al., 2017;Slukvin, Grendell, Rao, Hughes, & Golos, 2006), suggesting that similar immunological responses can be initiated in different primate species.

In addition to the above-described nonclassical MHC class I molecules that are conserved between humans and NHP, different NHP species appear to possess species-specific MHC genes that encode molecules that also have nonclassical features. An example is *Patr-AL*. This chimpanzee-specific *MHC-A*-like gene is present on approximately half of the chimpanzee MHC haplotypes (Geller et al., 2002), suggesting that the absence of the gene in homozygous animals is still compatible with life. Patr-AL transfection studies have illustrated that its distinctive cytoplasmic tail initiates the intracellular retention of the molecule, which results in low cell-surface expression (Goyos et al., 2015). Patr-AL has an overlapping peptide-binding repertoire with HLA-A2 (Gleimer et al., 2011), and it is suggested that it may fulfil a specialized function, although it is unclear why the gene then never reached fixation. In several macaque species and in the sooty mangabey (*Cercocebus atys*), an *MHC-B*-like gene, named *MHC-I*, can be found, which is characterized by low levels of polymorphism (de Groot et al., 2019;Heimbruch et al., 2015;Urvater et al., 2000). The gene seems to have arisen from a duplication event in the *MHC-B* block of OWM and is fixed. The function of the molecules encoded by the *MHC-I* gene is currently unknown. Based on its hybrid character, between classical and nonclassical MHC class I molecules, high levels of conservation, and the observation that it is detected mainly intracellularly (Rosner et al., 2010), it most likely fulfils an at present unknown specialized function.

3.3 | Organization of the MHC class II genes in primate species

The evolutionary equivalent of *HLA-DP*, *HLA-DQ* and *HLA-DR* genes is present in great apes, OWM and NWM species, although some exceptions are observed in the *DP* region of certain NWM

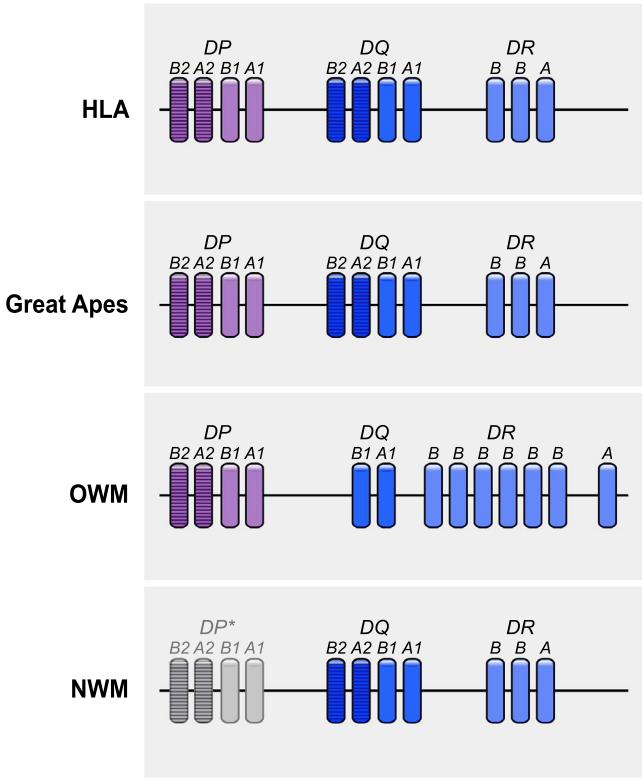


FIGURE 3 Schematic organization of the MHC class II region in humans (HLA), great apes, Old World monkey (OWM) and New World monkey (NWM). *The DP region in the common marmosets seems to be inactive, whereas this region is found to be active in the cotton-top tamarin and Nancy Ma's night monkey (Antunes et al., 1998;Bidwell et al., 1994;Diaz et al., 2002)

species (Figure 3) (Antunes et al., 1998;Bidwell et al., 1994;Bontrop, 2006;Diaz, Daubenberger, Zalac, Rodriguez, & Patarroyo, 2002). In humans, two *DPA*, *DPB*, *DQA* and *DQB* genes are present per haplotype. The *HLA-DPA1/DPB1* and *HLA-DQA1/DQB1* pairs encode functional products, which are expressed on the cell surface of professional antigen-presenting cells like B cells and dendritic cells. The *HLA-DQA2/DQB2* gene pair is also found to encode functional transcripts, but the corresponding proteins are expressed only on epidermal Langerhans cells (Lenormand et al., 2012). Great apes and NWM possess two *DPA*, *DPB*, *DQA* and *DQB* genes on a haplotype as well, whereas in OWM, the *DQA2* and *DQB2* genes have been deleted (Bontrop, 2006;Bontrop, Otting, de Groot, & Doxiadis, 1999). Functional transcripts for the *DPA1/DPB1* and *DQA1/DQB1* tandems are described in great apes, OWM and NWM.

The *HLA-DR* region comprises one *DRA* gene, whereas the *DRB* region shows copy number variation, and one to four genes/pseudogenes can be present per haplotype (Figure 4a). On a chromosome, the combination of different *DRB* genes, referred to as haplotype configuration, can be unique. Five *HLA-DR* haplotype configurations are encountered in humans, termed DR1, DR8, DR51, DR52, DR53, differing in gene content and its combinations (Marsh, Parham, & Barber, 2000). Great apes, OWM and NWM show disparate variation as regards DR haplotype configurations. For the great apes, chimpanzees in particular are studied extensively, and nine different DR haplotype configurations are known (de Groot et al., 2009). One *DRA* gene and two to five *DRB* genes/pseudogenes per haplotype can be present (Figure 4b). Humans and chimpanzees share the haplotype configuration containing the *DRB1*07/DRB7*01/DRB8/DRB4*01* genes, which in humans represents one of the DR53 haplotypes. Macaque and baboon species, as representatives of the OWM, possess many different DR haplotype configurations (Figure 4c). Each haplotype contains one *DRA* gene, but the number and content of *DRB* genes can vary extensively (Doxiadis et al., 2007;Doxiadis, de Vos-Rouweler, de Groot, Otting, & Bontrop, 2012). Two to six *DRB* genes/pseudogenes per haplotype can be encountered. *DRB6* is a pseudogene that is often present, and it is speculated that the retroviral element in this pseudogene may drive recombination, resulting in many different DR haplotype configurations (Doxiadis, de Groot, & Bontrop, 2008). In contrast, in common marmosets, an NWM species, only one DR haplotype configuration is reported, containing one *DRA* and three types of *DRB* genes (Figure 4d) (Antunes et al., 1998;Doxiadis et al., 2006). The *Caja-DRB* genes are either monomorphic or display only moderate levels of polymorphism, and one gene, *Caja-DRB1*03*, appeared to be a pseudogene. From this pseudogene, the characteristic EYSTS-motif, which is fundamental for the peptide-binding site, was "rescued" by a recombination event in common marmosets (Doxiadis et al., 2006).

Briefly, in general the organization of the MHC II region in humans and NHP is comparable. In particular, dissimilarities are observed in the total number of *DRB* genes present per haplotype, and one to four *DRB* genes can be transcribed per haplotype.

4 | MHC POLYMORPHISM: HUMANS VERSUS CHIMPANZEES AND RHESUS MACAQUES

4.1 | Reduced MHC repertoire in Pan species

Worldwide, over 1,200 human population studies have been performed concerning the characterization of the MHC repertoire (Gonzalez-Galarza et al., 2015). The IPD-IMGT/HLA database (Robinson et al., 2015) currently comprises data on 5,907 *HLA-A*, 7,126 *HLA-B*, 5,709 *-C*, 168 *HLA-DPA1*, 1,537 *HLA-DPB1*, 229 *HLA-DQA1*, 1,795 *HLA-DQB1*, 29 *HLA-DRA* and 3,331 *HLA-DRB* alleles (numbers are according release 3.39.0). For common chimpanzees, individuals of *P.t.verus*, *P.t.troglodytes* and *P.t.schweinfurthii* populations were studied for their MHC repertoire (de Groot et al., 2000;Maibach et al., 2017;Otting, de Groot, & Bontrop, 2019;Wroblewski et al., 2015). One has to realize, however, that for NHP no commercial MHC typing kits are available, and the MHC genes are studied independently. The characterization of the MHC in NHP may comprise family-related animals, which allows the definition of MHC haplotype. For chimpanzees, approximately 250 animals were studied for the MHC, but the number of genes studied per animal may vary. The IPD-MHC NHP database (de Groot et al., 2019;Maccari et al., 2017) archives 46 *Patr-A*, 88 *Patr-B*, 47 *Patr-C*, 10 *Patr-DPA1*, 34 *Patr-DPB1*, 11 *Patr-DQA1*, 13 *Patr-DQB1*, 5 *Patr-DRA* and 81 *Patr-DRB* alleles (numbers are according release 3.4.0.0). Although there is a considerable discrepancy between the total number of humans and chimpanzees analysed, a thorough population analysis demonstrated that chimpanzees experienced a selective sweep that targeted their MHC class I region (de Groot & Bontrop, 2013;de Groot et al., 2002). As a result, chimpanzees have a reduced MHC class I repertoire (Figure 5). The *Patr-A* alleles are only related to the evolutionary equivalents of the *HLA-A1/A3/A11/A30* family, whereas the equivalents of the other five *HLA-A* families (*HLA-A2*, *HLA-A9*, *HLA-A10*, *HLA-A19* and *HLA-A80*) are absent. Gorillas (≈35 animals were studied for their MHC class I variation), however, possess the evolutionary equivalents of the *HLA-A2* family (Hans et al., 2017;Lawlor et al., 1991). Therefore, this *HLA-A2* family originates from a shared ancestor of humans, chimpanzees and gorillas, and as such is lost in chimpanzees. Chimpanzees also have a reduced *B* and *C* repertoire (Figure 5) (de Groot & Bontrop, 2013) and show a reduction in the MHC class I chain-related gene (*MIC*) repertoire (de Groot et al., 2005). With regard to diminished levels of allelic polymorphism and lineages, this genetic footprint illustrates that chimpanzees experienced a selective sweep in their MHC class I repertoire. The question is whether this footprint extends to the MHC class II region. Indeed, for the MHC class II genes, chimpanzees also possess a relatively low number of lineages and alleles as compared to humans. For example, *Patr-DQA* and *Patr-DQB* alleles each cluster into three lineages, in contrast to the *HLA-DQA* and *HLA-DQB* alleles, that each cluster into six different lineages (Table 2). For the *DRB* region, in particular the total number of *HLA-DRB1* lineages exceeds the total number of *Patr-DRB1* lineages (Table 2). Chimpanzees

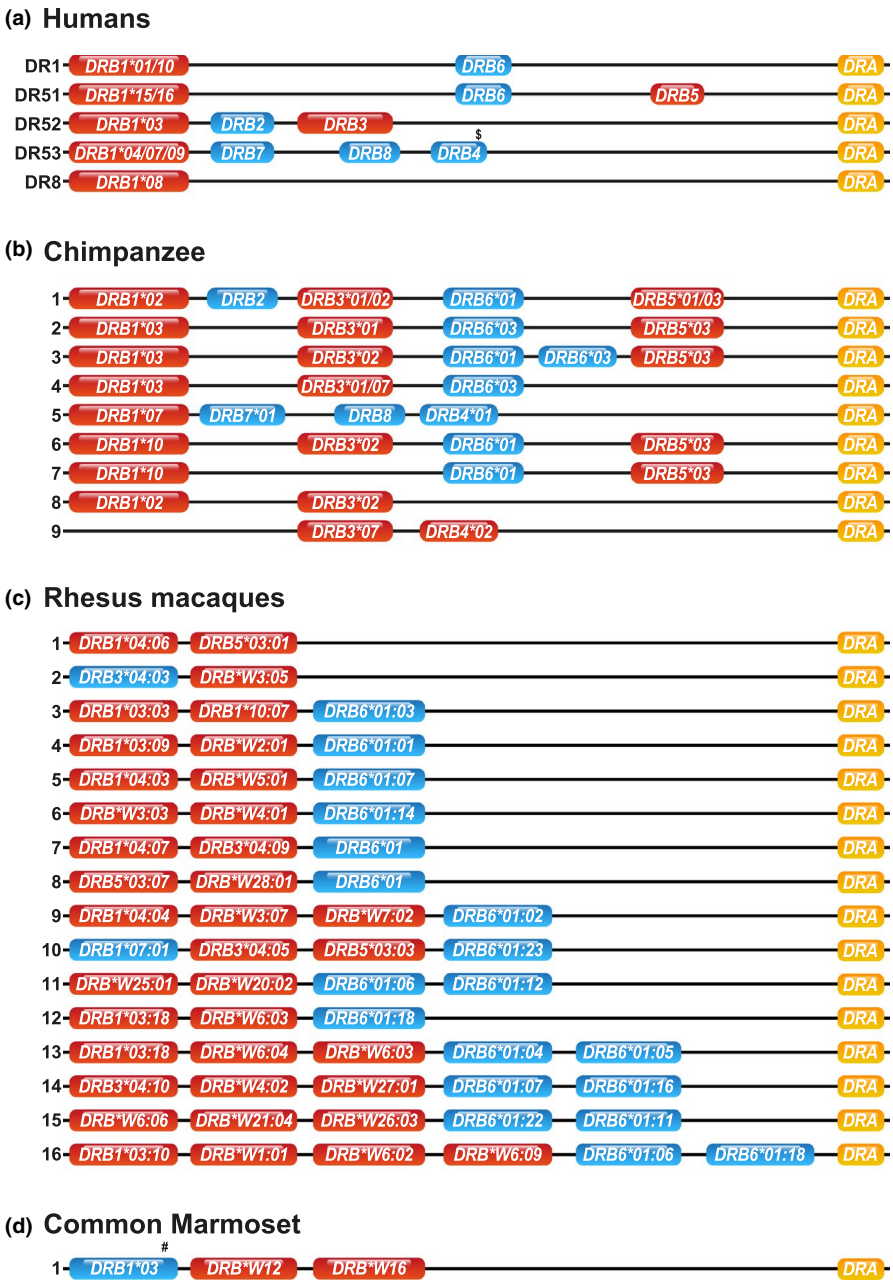


FIGURE 4 Schematic overview of *DR* haplotype configurations in (a) human, (b) chimpanzee, (c) rhesus macaque and (d) common marmoset. For the rhesus macaque, only a representative number of DR haplotype configurations is shown. The different functional *DRB* genes on a haplotype configuration are indicated in red boxes, whereas the blue boxes represent pseudogenes. Each haplotype configuration has a *DRA* gene present (yellow box). The different genes within a gene region are numbered sequentially in the order of description, and for NHP, wherever possible, the HLA nomenclature was followed. However, when it is not clear whether it is a different gene or that we are dealing with multiple lineages that belong to the same gene, a workshop (W) designation has been introduced. $On some haplotypes the *HLA-DRB4* gene is translated. #There are two transcripts detected that partially contain *Caja-DRB1*03*, which illustrates that occasionally this gene can be functional. In those two cases, the exon 2 part of the *DRB1*03* gene is placed in the *Caja-DRB*W16* gene backbone, most likely by exon shuffling, and the products were found to be highly transcribed (Doxiadis et al., 2006)

only possess *DRB1* alleles clustering into the *HLA-DRB1*03*, **07* and **10* lineage, and alleles clustering into the *HLA-DRB1*01*, **08*, **09*, **11* till **16* lineages have not been detected (de Groot et al., 2008, 2009;Otting et al., 2019). Moreover, the equivalent of the *HLA-DRB1*04* lineage, which is present in macaques and humans, and as such represents an old entity, was lost during chimpanzee evolution (de Groot et al., 2009). The *HLA-DPB1* genes seem to evolve rapidly. The concerted action of point mutations and the exchange of sequence motifs has resulted in the definition of over 1,500 *HLA-DPB1* alleles (https://www.ebi.ac.uk/ipd/imgt/hla/stats.html). The rapid evolution, however, hampered division of the *HLA-DPB1* alleles into distinct lineages, and most alleles received their own lineage name (*DPB1*01* to *DPB1*999*). In chimpanzees, only 34 *DPB1* alleles are defined, which cluster into three distinct lineages (Otting et al., 2019). The mechanism of frequent exchange of sequence motifs, which is the hallmark for the *HLA-DPB* genes, seems to be absent here. Although chimpanzees appear to possess a limited MHC class II repertoire as compared to humans, recent work highlighted that the limited number of alleles present are distributed maximally across different haplotypes by means of crossing-over processes. More in detail, in a group of chimpanzees (*P.t.verus*), which comprised 27 founders animals, a total number of 37 unique *DPA-DPB-DQA-DQB-DRA-DRB* haplotypes have been defined (Otting et al., 2019).

Recently, three independent research groups published elaborate work on the bonobo MHC class I repertoire (≈100 animals, but number of genes studied per animal may vary), and this has resulted in the characterization of 24 *Papa-A*, 33 *Papa-B* and 17 *Papa-C* alleles (de Groot, Heijmans, Helsen, et al., 2017;Maibach et al., 2017;Wroblewski et al., 2017). The selective sweep that targeted the chimpanzee MHC class I region was dated to have

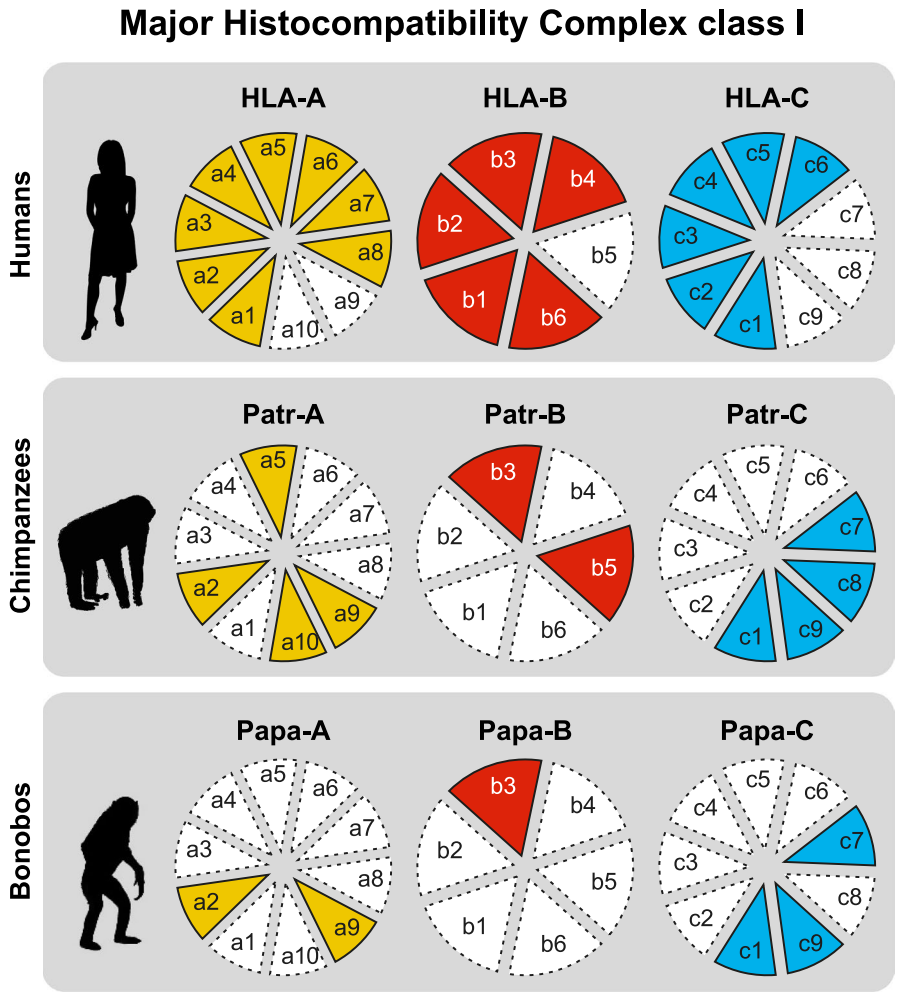


FIGURE 5 Pie charts illustrating the MHC class I intron 2 lineage distribution in human (HLA), chimpanzee (Patr) and bonobo (Papa) (adapted from Groot, Heijmans, & Bontrop, 2017). The influence of selection on the classical MHC class I genes has been studied by comparing intron 2 variation in humans and chimpanzee alleles in two well-defined populations (de Groot et al., 2002). The intron 2 lineages have been defined based on phylogenetic clustering of the different human and chimpanzee intron 2 alleles, and the presence of a particular intron 2 lineage (in *MHC-A* numbered a1-a10, in *MHC-B* b1-b6 and in *MHC-C* c1-c9) in a species is indicated by a coloured section in a pie. Statistical analyses showed that the intron 2 variation found in humans as compared to chimpanzees is 2.56 and 2.64 times higher for *MHC-A* and for *MHC-B*, respectively (de Groot et al., 2002). Subsequently, analyses on the difference in unique number of alleles (Δn_e) of MHC class I intron 2 revealed that for all three MHC class I genes (*A*, *B* and *C*), a statistical significant difference was observed for the Δn_e as well as for the ratio (number of unique alleles in humans divided by the number of unique alleles in chimpanzees) between humans and chimpanzees (de Groot & Bontrop, 2013), and substantiated that chimpanzees experienced a selective sweep targeting their MHC class I repertoire. Recently, MHC class I analyses (including exon 2, intron 2 and exon 3) was conducted in a panel of bonobos, and this revealed that this species shows an even more reduced MHC class I *B* intron 2 repertoire as compared to chimpanzees (de Groot, Heijmans, Helsen, et al., 2017)

happened approximately 2–3 million years ago (de Groot et al., 2002), before the speciation of chimpanzees and bonobos about 1.5 to 2 million years ago (Becquet et al., 2007;Prado-Martinez et al., 2013). Bonobos share a comparable MHC class I repertoire with that of chimpanzees (Figure 5) (de Groot, Heijmans, Helsen, et al., 2017), which further confirmed that the selective sweep took place before the speciation of these two species. However, bonobos appear to have an even more reduced MHC class I *B* repertoire than chimpanzees (Figure 5) (de Groot, Heijmans, Helsen, et al., 2017;Wroblewski et al., 2017). This suggests that after the selective sweep, bonobos experienced subsequent selective forces that have further shaped their MHC class I repertoire. Based on the functional characteristics of the present bonobo *MHC-B* repertoire, we recently put forward the hypothesis that a malaria-like parasite may be a candidate pathogen that has further shaped their MHC repertoire (de Groot, Stevens, & Bontrop, 2018).

One wonders what may have caused the initial selective sweep. In brief, chimpanzees appear to be relatively resistant to developing AIDS after experimental infection with human immunodeficiency virus type-1 (HIV-1) or natural infection with the chimpanzee-derived simian immunodeficiency virus (SIV_{cpz}) infection (de Groot, Heijmans, & Bontrop, 2017). In bonobos, infections with HIV-1/SIV have not been documented (Li et al., 2012). In humans, a relative resistance to developing AIDS correlates with the presence of particular HLA

TABLE 2 Overview of the *DRB*, *DQA* and *DQB* lineages in humans, chimpanzees (*Patr*) and rhesus macaques (*Mamu*)

Human	Chimpanzee	Rhesus macaque
HLA-DQA1*01	***Patr-DQA1*01***	***Mamu-DQA1*01***
*HLA-DQA1*02*		
*HLA-DQA1*03*		
*HLA-DQA1*04*		
HLA-DQA1*05	***Patr-DQA1*05***	***Mamu-DQA1*05***
*HLA-DQA1*06*		
	*Patr-DQA1*20*	
		*Mamu-DQA1*23*
		*Mamu-DQA1*24*
		*Mamu-DQA1*26*
*HLA-DQB1*02*		
HLA-DQB1*03	***Patr-DQB1*03***	
*HLA-DQB1*04*		
*HLA-DQB1*05*		
HLA-DQB1*06	***Patr-DQB1*06***	***Mamu-DQB1*06***
	*Patr-DQB1*15*	*Mamu-DQB1*15*
		*Mamu-DQB1*16*
		*Mamu-DQB1*17*
		*Mamu-DQB1*18*
		*Mamu-DQB1*24*
*HLA-DRB1*01*		
	*Patr-DRB1*02*	
HLA-DRB1*03	***Patr-DRB1*03***	***Mamu-DRB1*03***
HLA-DRB1*04	[a]	***Mamu-DRB1*04***
HLA-DRB1*07	***Patr-DRB1*07***	***Mamu-DRB1*07***
*HLA-DRB1*08*		
*HLA-DRB1*09*		
HLA-DRB1*10	***Patr-DRB1*10***	***Mamu-DRB1*10***
*HLA-DRB1*11*		
*HLA-DRB1*12*		
*HLA-DRB1*13*		
*HLA-DRB1*14*		
*HLA-DRB1*15*		
*HLA-DRB1*16*		
HLA-DRB3*01	***Patr-DRB3*01***	
HLA-DRB3*02	***Patr-DRB3*02***	
*HLA-DRB3*03*		
		*Mamu-DRB3*04*
	*Patr-DRB3*07*	
HLA-DRB4*01	***Patr-DRB4*01***	***Mamu-DRB4*01***
HLA-DRB4*02	***Patr-DRB4*02***	
*HLA-DRB4*03*		
HLA-DRB5*01	***Patr-DRB5*01***	
*HLA-DRB5*02*		
	*Patr-DRB5*03*	*Mamu-DRB5*03*
	*Patr-DRB*W*[b]	*Mamu-DRB*W*[b]

Note: Shared lineages between humans and chimpanzees or humans and rhesus macaques are indicated in boldface.

[a]During evolution, chimpanzees lost the equivalent of the *HLA-DRB1*04* lineage (de Groot et al., 2009).

[b]See the IPD-MHC NHP database for the different lineages.

allotypes, such as HLA-B*27/B*57 (Fellay et al., 2007;Goulder & Walker, 2012;Kiepiela et al., 2004). From a functional point of view, the reduced chimpanzee MHC class I repertoire encodes allotypes that have the capability of targeting conserved retroviral elements (Groot, Heijmans, & Bontrop, 2017;de Groot et al., 2010), and act in a way similar to that of the AIDS controlling HLA-B*27/B*57 allotypes in humans. Hence, the selective sweep in the MHC class I repertoire of chimpanzees was most likely caused by an ancestral retroviral infection that had similarities to HIV-1 (de Groot et al., 2010). This assumption is supported further by a recent investigation of CD4 receptor diversity in a large sample of wild chimpanzees (Bibollet-Ruche et al., 2019). CD4 is the primary receptor used by HIV-1/SIVs to enter the target cell. Although the D1 domain of the chimpanzee CD4 displays polymorphism, they are distributed differentially among the chimpanzee subspecies, and in such a way that the most logical explanation is that these polymorphisms have evolved in a common ancestor. Based on the lines of evidence that the selective sweep in the chimpanzee MHC class I was caused by an ancestral retroviral infection such as HIV-1/SIV_{cpz}, it has been suggested that different SIVs may as well have shaped the chimpanzee CD4 repertoire (Bibollet-Ruche et al., 2019).

4.2 | MHC polymorphism in rhesus macaques

Rhesus macaques are often used as a model species in biomedical research to study human diseases. In particular, they serve as models to evaluate HIV-1 vaccine candidates or vaccine components (Fauci et al., 2008;Watkins et al., 2008). But rhesus monkeys, for instance, are also used as preclinical models in rheumatoid arthritis and transplantation research (Bontrop, 2001;Vierboom, Jonker, Bontrop, & t Hart B, 2005). Within these models, knowledge regarding MHC polymorphism and its functional consequences may contribute in finding a rationale for the immune responses observed. Over the past few decades, the MHC has been studied extensively in rhesus macaques (> 5,000 individuals), mostly in animals of Indian or Chinese origin, and has resulted in the description of over 1,800 alleles belonging to 31 different genes (https://www.ebi.ac.uk/ipd/mhc/statistics). But other macaque species, such as the cynomolgus macaque (≈ 3,000 individuals) and southern pigtailed

macaques (*Macaca nemestrina*, *Mane*) (≈ 500 individuals), have also been investigated thoroughly, and more than 2,400 and 800 alleles belonging to 33 and 25 genes, respectively, have been assigned. When focussing on the classical MHC class I and II genes encoding the antigen presentation molecules, in rhesus macaques 245 *Mamu-A1*, 588 *Mamu-B*, 50 *Mamu-DPA1*, 66 *Mamu-DPB1*, 47 *Mamu-DQA1*, 79 *Mamu-DQB1*, 28 *Mamu-DRA* and 261 *Mamu-DRB* alleles have been documented (numbers are according release 3.4.0.0) (de Groot et al., 2019;Maccari et al., 2017). The *Mamu-A1* and *Mamu-B* alleles have been subject to expansion, form their own monophyletic groups and do not cluster together with human or great ape *Mhc* class I *A* and *B* alleles, respectively (de Groot et al., 2012). Intermingling with *A1* and *B* alleles of other macaque species is frequently observed (de Groot et al., 2012). Although the human and macaque class I alleles do not show a close phylogenetic relationship at the sequence level, similarities are observed when functional characteristics of the allotypes, such as peptide-binding profiles, are considered. The peptide-binding cleft of an MHC class I molecule is tight, is encoded by exons 2 and 3 of the MHC class I gene and consists of six different pockets, designated A to F. Several HLA-A and HLA-B allotypes are clustered into supertypes based on their functional characteristics and the amino acid composition of their B and F pockets (Sidney, Peters, Frahm, Brander, & Sette, 2008). The B and F pockets usually bind the anchor residues of the peptides, although there are many exceptions to this rule. In general, MHC class I molecules bind peptides nine amino acids in length, in which the amino acids at the second position and at the C-terminal end bind into the B and F pocket, respectively. Six different HLA-A and six different HLA-B supertypes are recognized, all of which have their own specific chemical characteristic at the B and F pocket (Table 3). For 24 Mamu-A and Mamu-B allotypes, the peptide-binding motifs are known (Allen et al., 1998;Dzuris et al., 2000;de Groot et al., 2013;de Groot, Heijmans, de Ru, et al., 2017;Hickman-Miller et al., 2005;Loffredo et al., 2009;Mothe et al., 2013;Reed et al., 2011;Sette et al., 2012;Solomon et al., 2010;Southwood et al., 2011), and although many of them have unique features, some share features with the HLA supertypes A02, A03, B07, B27 and B44 (Table 3). Therefore, human and rhesus macaque MHC class I molecules may select the same processed peptides for activating the immune response, thereby proving the relevance of rhesus macaques as preclinical models.

An overview of the *DQA/DQB* and *DRB* lineages present in rhesus macaques is provided (Table 2). Rhesus macaques possess evolutionary equivalents of the *HLA-DQA1*01*, **05*, *HLA-DQB1*06*, *HLA-DRB1*03*, **04*, **07*, **10* and *HLA-DRB4*01* lineages (Table 2). For the *DP* genes, the trans-species mode of evolution is not supported for humans and rhesus macaques. Rhesus macaques show polymorphism at the *DPA1* gene, and 50 *Mamu-DPA1* alleles are defined, which cluster into eight distinct lineages (designated *Mamu-DPA1*02*, **04*, **06*, **07*, **08*, **09*, **10*, **11*). The rhesus macaque *DPB1*

TABLE 3 HLA-A and HLA-B supertype classification

HLA supertype	Chemical specificity		Rhesus macaque
	B pocket	F pocket	
A01	Small and aliphatic	Aromatic and large hydrophobic	
A01A03	Small and aliphatic	Aromatic and basic	
A01A24	Small, aliphatic and aromatic	Aromatic and large hydrophobic	
A02	Small and aliphatic	Aliphatic and small hydrophobic	+
A03	Small and aliphatic	Basic	+
A24	Aromatic and aliphatic	Aromatic, aliphatic and hydrophobic	
B07	Proline	Aromatic, aliphatic and hydrophobic	+
B08	Undefined	Aromatic, aliphatic and hydrophobic	
B27	Basic	Aromatic, aliphatic, basic and hydrophobic	+
B44	Acidic	Aromatic, aliphatic and hydrophobic	+
B58	Small	Aromatic, aliphatic and hydrophobic	
B62	Aliphatic	Aromatic, aliphatic and hydrophobic	

Note: Indicated are the specific chemical properties of the preferred amino acids for the B and F pocket (adapted from Sidney et al., 2008). A plus sign (+) indicates whether rhesus macaque MHC class I molecules are detected that share features with the indicated HLA supertypes.

alleles can also be grouped into lineages, with 20 at present (Otting et al., 2017). Of note, 120 *Mamu-DRB* alleles are denoted at present by a workshop (W) designation, as it is unclear whether these alleles are encoded by different genes or represent multiple lineages of one and the same gene (de Groot et al., 2012). An example of conservation of function in MHC class II is provided by the members of the trans-species *-DRB1*03* lineage. Two unique motifs, EYSTS at position 9–13 and YLDRYF at position 26–31, are shared between human, chimpanzee and rhesus macaque DRB1*03 lineage members. These motifs play a crucial role in binding the p3-13 peptide of 65-kD heat-shock protein (hsp65) of *Mycobacterium leprae* and *M. tuberculosis* (Geluk et al., 1993). Moreover, HLA-DRB1*03-restricted T cells have been shown to recognize the p3-13 hsp65 peptide in the context of rhesus macaque antigen-presenting cells, illustrating that next to conservation in the antigen-binding site, also recognition by the T-cell receptor can be conserved across species barrier (Geluk et al., 1993).

5 | CONCLUDING REMARKS

The general picture that emerges is that humans and NHP share a comparable MHC class I and II region and repertoire, and this is most robust for those species that show the closest evolutionary relationship to humans (Figures 2a and 3). Studies in NHP showed us that certain MHC polymorphisms are very old, and sharing of genes and lineages is common in humans, chimpanzees and rhesus macaques (Table 2). In addition, from the comparison of the MHC region between humans and NHP, we have learned that particular sections of the region are highly plastic. This plasticity can be found in the diversity of the region, resulting in the expansion or contraction of the number of genes present on a haplotype. In addition, plasticity is reflected by the functional characteristics of different MHC molecules: for example, Caja-G, which executes a classical antigen presentation function compared to the nonclassical HLA-G molecule.

HLA-C molecules can be divided into two groups depending on the KIR epitope that is present. A C1 and C2 group are recognized, and the distinction is defined by a dimorphism at position 80 at the alpha 1 domain. Comparative genetic studies in different primate species showed that the *C* gene evolved from a duplication event of a *B* allele that encoded a C1-epitope and that this epitope could have already been present in the ancestor of catarrhine species (Guethlein, Norman, Hilton, & Parham, 2015). MHC-C allotypes that contain a C2-epitope are also present in chimpanzees and gorillas. The *MHC-C* gene reached fixation in a progenitor species of the human, chimpanzee, gorilla lineage, and these species show a further diversification of their KIRs in the direction of specific C1 or C2 receptors (Wroblewski, Parham, & Guethlein, 2019). In particular, HLA-C seems to have evolved to become the dominant KIR ligand for NK cell education and to finetune the NK cell activity. Another distinction between humans and NHP is observed with regard to the DR region (Figure 4). Five HLA-DR haplotype configurations are known, all showing a considerable allelic polymorphism, in particular at the *-DRB1* gene (Marsh et al., 2000;Robinson et al., 2020). In contrast, macaque species have many different DR haplotype configurations (>30), which themselves display only a limited degree of allelic polymorphism (Doxiadis, Otting, de Groot, Noort, & Bontrop, 2000;Doxiadis et al., 2012;Khazand, Peiberg, Nagy, & Sauermann, 1999). The common marmoset represents the other end of the spectrum, as only one DR haplotype configuration is encountered (Doxiadis et al., 2006). This species has overall a limited level of MHC class II variability (Antunes et al., 1998), and animals living in captivity were shown to be highly susceptible and prone to dying from certain bacterial and helminth infections (Potkay, 1992). The above-mentioned examples illustrate that during evolution, humans and NHP developed different strategies to generate various types of levels of polymorphisms at the population level to cope with pathogens.

The main premise is that MHC polymorphism prevents an entire population from becoming extinct by means of only a single pathogen. In this perspective, the maintenance of MHC diversity may be of benefit to a species, and therefore, the characterization of the MHC polymorphism in NHP populations is a valuable tool for conservation biology purposes. Nevertheless, one has to consider that there are examples of NHP species described that have very limited MHC polymorphism, such as the West African chimpanzee, bonobo and common marmoset, which, however, are shown to produce offspring and can survive in their natural habitat.

Worldwide, macaque species are used most often as animal models to study various human diseases: for instance, to test the safety and efficacy of new vaccines against a disease like AIDS caused by HIV-1. Although this review has illustrated that the organization of the human and macaque MHC class I and II region seem to have its own specificities: for example, macaques show expansion in the number of MHC class I *A* and *B* genes, and the equivalent of a *C* gene is absent (Figure 2a). Similarity is observed in the functional characteristics of particular macaque A and B molecules when compared to HLA-A and HLA-B, and this supports the rationales for using this type of primate species in preclinical research.

Future studies focussing on increasing our knowledge with respect to MHC polymorphism in NHP will provide further insights into how different primate species/populations have evolved, and how evolution may have shaped the HLA system. Moreover, research that increases knowledge regarding the functional characteristics of the various genes in different NHP will contribute to a better understanding of the immunological responses observed in a species and of how this compares to the responses observed in humans.

ACKNOWLEDGMENTS

The authors would like to thank D. Devine for editing the manuscript, J. Bruijnesteijn for the constructive feedback and F. van Hassel for the artwork.

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REFERENCES

Abi-Rached, L., Moesta, A. K., Rajalingam, R., Guethlein, L. A., & Parham, P. (2010). Human-specific evolution and adaptation led to major qualitative differences in the variable receptors of human and chimpanzee natural killer cells. *PLoS Genetics*, *6*, e1001192. https://doi.org/10.1371/journal.pgen.1001192

Adams, E. J., Cooper, S., & Parham, P. (2001). A novel, nonclassical MHC class I molecule specific to the common chimpanzee. *The Journal of Immunology*, *167*, 3858–3869. https://doi.org/10.4049/jimmunol.167.7.3858

Adams, E. J., Thomson, G., & Parham, P. (1999). Evidence for an HLA-C-like locus in the orangutan Pongo pygmaeus. *Immunogenetics*, *49*, 865–871. https://doi.org/10.1007/s002510050566

Allen, T. M., Sidney, J., del Guercio, M. F., Glickman, R. L., Lensmeyer, G. L., Wiebe, D. A., … Watkins, D. I. (1998). Characterization of the peptide binding motif of a rhesus MHC class I molecule (Mamu-A*01) that binds an immunodominant CTL epitope from simian immunodeficiency virus. *The Journal of Immunology*, *160*, 6062–6071.

Antunes, S. G., de Groot, N. G., Brok, H., Doxiadis, G., Menezes, A. A., Otting, N., & Bontrop, R. E. (1998). The common marmoset: A new world primate species with limited Mhc class II variability. *Proceedings of the National Academy of Sciences of the United States of America*, *95*, 11745–11750. https://doi.org/10.1073/pnas.95.20.11745

Arguello-Sanchez, L. E., Arguello, J. R., Garcia-Feria, L. M., Garcia-Sepulveda, C. A., Santiago-Alarcon, D., & Espinosa de los Monteros, A. (2018). MHC class II DRB variability in wild black howler monkeys (Alouatta pigra), an endangered New World primate. *Animal Biodiversity and Conservation*, *41*, 389–404. https://doi.org/10.32800/abc.2018.41.0389

Becquet, C., Patterson, N., Stone, A. C., Przeworski, M., & Reich, D. (2007). Genetic structure of chimpanzee populations. *PLoS Genetics*, *3*, e66. https://doi.org/10.1371/journal.pgen.0030066

Bibollet-Ruche, F., Russell, R. M., Liu, W., Stewart-Jones, G. B. E., Sherrill-Mix, S., Li, Y., … Hahn, B. H. (2019). CD4 receptor diversity in chimpanzees protects against SIV infection. *Proceedings of the National Academy of Sciences of the United States of America*, *116*, 3229–3238. https://doi.org/10.1073/pnas.1821197116

Bidwell, J. L., Lu, P., Wang, Y., Zhou, K., Clay, T. M., & Bontrop, R. E. (1994). DRB, DQA, DQB and DPB nucleotide sequences of Saguinus oedipus B95–8. *European Journal of Immunogenetics*, *21*, 67–77.

Blokhuis, J. H., van der Wiel, M. K., Doxiadis, G. G., & Bontrop, R. E. (2009). Evidence for balancing selection acting on KIR2DL4 genotypes in rhesus macaques of Indian origin. *Immunogenetics*, *61*, 503–512. https://doi.org/10.1007/s00251-009-0379-6

Bontrop, R. E. (2001). Non-human primates: Essential partners in biomedical research. *Immunological Reviews*, *183*, 5–9. https://doi.org/10.1034/j.1600-065x.2001.1830101.x

Bontrop, R. E. (2006). Comparative genetics of MHC polymorphisms in different primate species: Duplications and deletions. *Human Immunology*, *67*, 388–397. https://doi.org/10.1016/j.humimm.2006.03.007

Bontrop, R. E., Otting, N., de Groot, N. G., & Doxiadis, G. G. (1999). Major histocompatibility complex class II polymorphisms in primates. *Immunological Reviews*, *167*, 339–350. https://doi.org/10.1111/j.1600-065X.1999.tb01403.x

Boyson, J. E., Iwanaga, K. K., Golos, T. G., & Watkins, D. I. (1997). Identification of a novel MHC class I gene, Mamu-AG, expressed in the placenta of a primate with an inactivated G locus. *The Journal of Immunology*, *159*, 3311–3321.

Boyson, J. E., McAdam, S. N., Gallimore, A., Golos, T. G., Liu, X., Gotch, F. M., … Watkins, D. I. (1995). The MHC E locus in macaques is polymorphic and is conserved between macaques and humans. *Immunogenetics*, *41*, 59–68. https://doi.org/10.1007/BF00182314

Braud, V. M., Allan, D. S., O'Callaghan, C. A., Soderstrom, K., D'Andrea, A., Ogg, G. S., … McMichael, A. J. (1998). HLA-E binds to natural killer cell receptors CD94/NKG2A, B and C. *Nature*, *391*, 795–799. https://doi.org/10.1038/35869

Braud, V., Jones, E. Y., & McMichael, A. (1997). The human major histocompatibility complex class Ib molecule HLA-E binds signal sequence-derived peptides with primary anchor residues at positions 2 and 9. *European Journal of Immunology*, *27*, 1164–1169. https://doi.org/10.1002/eji.1830270517

Brown, J. H., Jardetzky, T., Saper, M. A., Samraoui, B., Bjorkman, P. J., & Wiley, D. C. (1988). A hypothetical model of the foreign antigen binding site of class II histocompatibility molecules. *Nature*, *332*, 845–850. https://doi.org/10.1038/332845a0

Burian, A., Wang, K. L., Finton, K. A., Lee, N., Ishitani, A., Strong, R. K., & Geraghty, D. E. (2016). HLA-F and MHC-I open conformers bind natural killer cell Ig-like receptor KIR3DS1. *PLoS ONE*, *11*, e0163297. https://doi.org/10.1371/journal.pone.0163297

Burrows, C. K., Kosova, G., Herman, C., Patterson, K., Hartmann, K. E., Velez Edwards, D. R., … Ober, C. (2016). Expression quantitative trait locus mapping studies in mid-secretory phase endometrial cells identifies HLA-F and TAP2 as fecundability-associated genes. *PLoS Genetics*, *12*, e1005858. https://doi.org/10.1371/journal.pgen.1005858

Canavez, F., Young, N. T., Guethlein, L. A., Rajalingam, R., Khakoo, S. I., Shum, B. P., & Parham, P. (2001). Comparison of chimpanzee and human leukocyte Ig-like receptor genes reveals framework and rapidly evolving genes. *The Journal of Immunology*, *167*, 5786–5794. https://doi.org/10.4049/jimmunol.167.10.5786

Cao, Y. H., Fan, J. W., Li, A. X., Liu, H. F., Li, L. R., Zhang, C. L., … Sun, Z. Z. (2015). Identification of MHC I class genes in two Platyrrhini species. *American Journal of Primatology*, *77*, 527–534. https://doi.org/10.1002/ajp.22372

Chen, Z. W., McAdam, S. N., Hughes, A. L., Dogon, A. L., Letvin, N. L., & Watkins, D. I. (1992). Molecular cloning of orangutan and gibbon MHC class I cDNA. The HLA-A and -B loci diverged over 30 million years ago. *The Journal of Immunology*, *148*, 2547–2554.

Daza-Vamenta, R., Glusman, G., Rowen, L., Guthrie, B., & Geraghty, D. E. (2004). Genetic divergence of the rhesus macaque major histocompatibility complex. *Genome Research*, *14*, 1501–1515. https://doi.org/10.1101/gr.2134504

de Groot, N. G., & Bontrop, R. E. (2013). The HIV-1 pandemic: Does the selective sweep in chimpanzees mirror humankind's future? *Retrovirology*, *10*, 53. https://doi.org/10.1186/1742-4690-10-53

de Groot, N. G., Garcia, C. A., Verschoor, E. J., Doxiadis, G. G., Marsh, S. G., Otting, N., & Bontrop, R. E. (2005). Reduced MIC gene repertoire variation in West African chimpanzees as compared to humans. *Molecular Biology and Evolution*, *22*, 1375–1385. https://doi.org/10.1093/molbev/msi127

de Groot, N. G., Heijmans, C. M. C., & Bontrop, R. E. (2017). AIDS in chimpanzees: The role of MHC genes. *Immunogenetics*, *69*, 499–509. https://doi.org/10.1007/s00251-017-1006-6

de Groot, N. G., Heijmans, C. M., de Groot, N., Doxiadis, G. G., Otting, N., & Bontrop, R. E. (2009). The chimpanzee Mhc-DRB region revisited: Gene content, polymorphism, pseudogenes, and transcripts. *Molecular Immunology*, *47*, 381–389. https://doi.org/10.1016/j.molimm.2009.09.003

de Groot, N. G., Heijmans, C. M., de Groot, N., Otting, N., de Vos-Rouweller, A. J., Remarque, E. J., … Bontrop, R. E. (2008). Pinpointing a selective sweep to the chimpanzee MHC class I region by comparative genomics. *Molecular Ecology*, *17*, 2074–2088. https://doi.org/10.1111/j.1365-294X.2008.03716.x

de Groot, N. G., Heijmans, C. M., de Ru, A. H., Hassan, C., Otting, N., Doxiadis, G. G., … Bontrop, R. E. (2013). Unique peptide-binding

motif for Mamu-B*037:01: An MHC class I allele common to Indian and Chinese rhesus macaques. *Immunogenetics*, *65*, 897–900. https://doi.org/10.1007/s00251-013-0734-5

de Groot, N. G., Heijmans, C. M. C., de Ru, A. H., Janssen, G. M. C., Drijfhout, J. W., Otting, N., … Bontrop, R. E. (2017). A specialist macaque MHC Class I molecule with HLA-B*27-like peptide-binding characteristics. *The Journal of Immunology*, *199*, 3679–3690. https://doi.org/10.4049/jimmunol.1700502

de Groot, N. G., Heijmans, C. M. C., Helsen, P., Otting, N., Pereboom, Z., Stevens, J. M. G., & Bontrop, R. E. (2017). Limited MHC class I intron 2 repertoire variation in bonobos. *Immunogenetics*, *69*, 677–688. https://doi.org/10.1007/s00251-017-1010-x

de Groot, N. G., Heijmans, C. M., van der Wiel, M. K., Blokhuis, J. H., Mulder, A., Guethlein, L. A., … Bontrop, R. E. (2016). Complex MHC class I gene transcription profiles and their functional impact in orangutans. *The Journal of Immunology*, *196*, 750–758. https://doi.org/10.4049/jimmunol.1500820

de Groot, N. G., Heijmans, C. M., Zoet, Y. M., de Ru, A. H., Verreck, F. A., van Veelen, P. A., … Bontrop, R. E. (2010). AIDS-protective HLA-B*27/B*57 and chimpanzee MHC class I molecules target analogous conserved areas of HIV-1/SIVcpz. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 15175–15180. https://doi.org/10.1073/pnas.1009136107

de Groot, N. G., Otting, N., Arguello, R., Watkins, D. I., Doxiadis, G. G., Madrigal, J. A., & Bontrop, R. E. (2000). Major histocompatibility complex class I diversity in a West African chimpanzee population: Implications for HIV research. *Immunogenetics*, *51*, 398–409. https://doi.org/10.1007/s002510050638

de Groot, N. G., Otting, N., Doxiadis, G. G., Balla-Jhagjhoorsingh, S. S., Heeney, J. L., van Rood, J. J., … Bontrop, R. E. (2002). Evidence for an ancient selective sweep in the MHC class I gene repertoire of chimpanzees. *Proceedings of the National Academy of Sciences of the United States of America*, *99*, 11748–11753. https://doi.org/10.1073/pnas.182420799

de Groot, N. G., Otting, N., Maccari, G., Robinson, J., Hammond, J. A., Blancher, A., … Bontrop, R. E. (2020). Nomenclature report 2019: Major histocompatibility complex genes and alleles of Great and Small Ape and Old and New World monkey species. *Immunogenetics*, *72*, 25–36.

de Groot, N. G., Otting, N., Robinson, J., Blancher, A., Lafont, B. A., Marsh, S. G., … Bontrop, R. E. (2012). Nomenclature report on the major histocompatibility complex genes and alleles of Great Ape, Old and New World monkey species. *Immunogenetics*, *64*, 615–631. https://doi.org/10.1007/s00251-012-0617-1

de Groot, N. G., Stevens, J. M. G., & Bontrop, R. E. (2018). Does the MHC Confer Protection against Malaria in Bonobos? *Trends in Immunology*, *39*, 768–771. https://doi.org/10.1016/j.it.2018.07.004

Denzin, L. K., & Cresswell, P. (1995). HLA-DM induces CLIP dissociation from MHC class II alpha beta dimers and facilitates peptide loading. *Cell*, *82*, 155–165.

Diaz, D., Daubenberger, C. A., Zalac, T., Rodriguez, R., & Patarroyo, M. E. (2002). Sequence and expression of MHC-DPB1 molecules of the New World monkey *Aotus nancymaae*, a primate model for Plasmodium falciparum. *Immunogenetics*, *54*, 251–259. https://doi.org/10.1007/s00251-002-0466-4

Doxiadis, G. G., de Groot, N., & Bontrop, R. E. (2008). Impact of endogenous intronic retroviruses on major histocompatibility complex class II diversity and stability. *Journal of Virology*, *82*, 6667–6677. https://doi.org/10.1128/JVI.00097-08

Doxiadis, G. G., de Groot, N., Claas, F. H., Doxiadis, I. I., van Rood, J. J., & Bontrop, R. E. (2007). A highly divergent microsatellite facilitating fast and accurate DRB haplotyping in humans and rhesus macaques. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 8907–8912. https://doi.org/10.1073/pnas.0702964104

Doxiadis, G. G., de Groot, N., Otting, N., de Vos-Rouweler, A. J., Bolijn, M. J., Heijmans, C. M., … Bontrop, R. E. (2013). Haplotype diversity generated by ancient recombination-like events in the MHC of Indian rhesus macaques. *Immunogenetics*, *65*, 569–584. https://doi.org/10.1007/s00251-013-0707-8

Doxiadis, G. G., de Vos-Rouweler, A. J., de Groot, N., Otting, N., & Bontrop, R. E. (2012). DR haplotype diversity of the cynomolgus macaque as defined by its transcriptome. *Immunogenetics*, *64*, 31–37. https://doi.org/10.1007/s00251-011-0561-5

Doxiadis, G. G., Otting, N., de Groot, N. G., Noort, R., & Bontrop, R. E. (2000). Unprecedented polymorphism of Mhc-DRB region configurations in rhesus macaques. *The Journal of Immunology*, *164*, 3193–3199.

Doxiadis, G. G. M., van der Wiel, M. K. H., Brok, H. P. M., de Groot, N. G., Otting, N., 't Hart, B. A., … Bontrop, R. E. (2006). Reactivation by exon shuffling of a conserved HLA-DR3-like pseudogene segment in a New World primate species. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 5864–5868. https://doi.org/10.1073/pnas.0600643103

Dulberger, C. L., McMurtrey, C. P., Holzemer, A., Neu, K. E., Liu, V., Steinbach, A. M., … Adams, E. J. (2017). Human leukocyte antigen F presents peptides and regulates immunity through interactions with NK cell receptors. *Immunity*, *46*(1018–1029), e1017. https://doi.org/10.1016/j.immuni.2017.06.002

Dzuris, J. L., Sidney, J., Appella, E., Chesnut, R. W., Watkins, D. I., & Sette, A. (2000). Conserved MHC class I peptide binding motif between humans and rhesus macaques. *The Journal of Immunology*, *164*, 283–291. https://doi.org/10.4049/jimmunol.164.1.283

Falk, K., Rotzschke, O., Stevanovic, S., Jung, G., & Rammensee, H. G. (1991). Allele-specific motifs revealed by sequencing of self-peptides eluted from MHC molecules. *Nature*, *351*, 290–296. https://doi.org/10.1038/351290a0

Fauci, A. S., Johnston, M. I., Dieffenbach, C. W., Burton, D. R., Hammer, S. M., Hoxie, J. A., … Greene, W. C. (2008). HIV vaccine research: The way forward. *Science*, *321*, 530–532. https://doi.org/10.1126/science.1161000

Fellay, J., Shianna, K. V., Ge, D., Colombo, S., Ledergerber, B., Weale, M., … Goldstein, D. B. (2007). A whole-genome association study of major determinants for host control of HIV-1. *Science*, *317*, 944–947. https://doi.org/10.1126/science.1143767

Fitch, Z., Schmitz, R., Kwun, J., Hering, B., Madsen, J., & Knechtle, S. J. (2019). Transplant research in nonhuman primates to evaluate clinically relevant immune strategies in organ transplantation. *Transplantation Reviews*, *33*, 115–129. https://doi.org/10.1016/j.trre.2019.03.002

Francke, U., & Pellegrino, M. A. (1977). Assignment of the major histocompatibility complex to a region of the short arm of human chromosome 6. *Proceedings of the National Academy of Sciences of the United States of America*, *74*, 1147–1151. https://doi.org/10.1073/pnas.74.3.1147

Fujiyama, A., Watanabe, H., Toyoda, A., Taylor, T. D., Itoh, T., Tsai, S. F., … Sakaki, Y. (2002). Construction and analysis of a human-chimpanzee comparative clone map. *Science*, *295*, 131–134. https://doi.org/10.1126/science.1065199

Garcia-Beltran, W. F., Holzemer, A., Martrus, G., Chung, A. W., Pacheco, Y., Simoneau, C. R., … Altfeld, M. (2016). Open conformers of HLA-F are high-affinity ligands of the activating NK-cell receptor KIR3DS1. *Nature Immunology*, *17*, 1067–1074. https://doi.org/10.1038/ni.3513

Geller, R., Adams, E. J., Guethlein, L. A., Little, A. M., Madrigal, J. A., & Parham, P. (2002). Linkage of Patr-AL to Patr-A and- B in the major histocompatibility complex of the common chimpanzee (Pan troglodytes). *Immunogenetics*, *54*, 212–215. https://doi.org/10.1007/s00251-002-0452-x

Geluk, A., Elferink, D. G., Slierendregt, B. L., van Meijgaarden, K. E., de Vries, R. R., Ottenhoff, T. H., & Bontrop, R. E. (1993). Evolutionary

conservation of major histocompatibility complex-DR/peptide/T cell interactions in primates. *Journal of Experimental Medicine*, *177*, 979–987. https://doi.org/10.1084/jem.177.4.979

Glazier, K. S., Hake, S. B., Tobin, H. M., Chadburn, A., Schattner, E. J., & Denzin, L. K. (2002). Germinal center B cells regulate their capability to present antigen by modulation of HLA-DO. *Journal of Experimental Medicine*, *195*, 1063–1069. https://doi.org/10.1084/jem.20012059

Glazko, G. V., & Nei, M. (2003). Estimation of divergence times for major lineages of primate species. *Molecular Biology and Evolution*, *20*, 424–434. https://doi.org/10.1093/molbev/msg050

Gleimer, M., Wahl, A. R., Hickman, H. D., Abi-Rached, L., Norman, P. J., Guethlein, L. A., … Parham, P. (2011). Although divergent in residues of the peptide binding site, conserved chimpanzee Patr-AL and polymorphic human HLA-A*02 have overlapping peptide-binding repertoires. *The Journal of Immunology*, *186*, 1575–1588. https://doi.org/10.4049/jimmunol.1002990

González-Galarza, F. F., Takeshita, L. Y. C., Santos, E. J. M., Kempson, F., Maia, M. H. T., Silva, A. L. S., … Middleton, D. (2015). Allele frequency net 2015 update: New features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. *Nucleic Acids Research*, *43*, D784–D788. https://doi.org/10.1093/nar/gku1166

Goulder, P. J., & Walker, B. D. (2012). HIV and HLA class I: An evolving relationship. *Immunity*, *37*, 426–440. https://doi.org/10.1016/j.immuni.2012.09.005

Goyos, A., Guethlein, L. A., Horowitz, A., Hilton, H. G., Gleimer, M., Brodsky, F. M., & Parham, P. (2015). A distinctive cytoplasmic tail contributes to low surface expression and intracellular retention of the Patr-AL MHC class I molecule. *The Journal of Immunology*, *195*, 3725–3736. https://doi.org/10.4049/jimmunol.1500397

Greene, J. M., Wiseman, R. W., Lank, S. M., Bimber, B. N., Karl, J. A., Burwitz, B. J., … O'Connor, D. H. (2011). Differential MHC class I expression in distinct leukocyte subsets. *BMC Immunology*, *12*, *39*. https://doi.org/10.1186/1471-2172-12-39

Groves, C. P. (2005). Order primates. In D. E. Wilson, & D. M. Reeder (Eds.), *Mammal species of the world* (pp. 111–184), 3rd ed. Baltimore: The Johns Hopkins University Press.

Guethlein, L. A., Norman, P. J., Heijmans, C. M., de Groot, N. G., Hilton, H. G., Babrzadeh, F., … Parham, P. (2017). Two Orangutan Species Have Evolved Different KIR Alleles and Haplotypes. *The Journal of Immunology*, *198*, 3157–3169.

Guethlein, L. A., Norman, P. J., Hilton, H. G., & Parham, P. (2015). Co-evolution of MHC class I and variable NK cell receptors in placental mammals. *Immunological Reviews*, *267*, 259–282. https://doi.org/10.1111/imr.12326

Hans, J. B., Bergl, R. A., & Vigilant, L. (2017). Gorilla MHC class I gene and sequence variation in a comparative context. *Immunogenetics*, *69*, 303–323. https://doi.org/10.1007/s00251-017-0974-x

Heimbruch, K. E., Karl, J. A., Wiseman, R. W., Dudley, D. M., Johnson, Z., Kaur, A., & O'Connor, D. H. (2015). Novel MHC class I full-length allele and haplotype characterization in sooty mangabeys. *Immunogenetics*, *67*, 437–445. https://doi.org/10.1007/s00251-015-0847-0

Hickman-Miller, H. D., Bardet, W., Gilb, A., Luis, A. D., Jackson, K. W., Watkins, D. I., & Hildebrand, W. H. (2005). Rhesus macaque MHC class I molecules present HLA-B-like peptides. *The Journal of Immunology*, *175*, 367–375. https://doi.org/10.4049/jimmunol.175.1.367

Joosten, S. A., van Meijgaarden, K. E., van Weeren, P. C., Kazi, F., Geluk, A., Savage, N. D., … Ottenhoff, T. H. (2010). Mycobacterium tuberculosis peptides presented by HLA-E molecules are targets for human CD8 T-cells with cytotoxic as well as regulatory activity. *PLoS Path*, *6*, e1000782. https://doi.org/10.1371/journal.ppat.1000782

Karl, J. A., Bohn, P. S., Wiseman, R. W., Nimityongskul, F. A., Lank, S. M., Starrett, G. J., & O'Connor, D. H. (2013) Major histocompatibility complex class I haplotype diversity in Chinese rhesus macaques. *G3 (Bethesda) 3*:1195–1201.

Kasahara, M., Suzuki, T., & Pasquier, L. D. (2004). On the origins of the adaptive immune system: Novel insights from invertebrates and cold-blooded vertebrates. *Trends in Immunology*, *25*, 105–111. https://doi.org/10.1016/j.it.2003.11.005

Kawamoto, Y., Takemoto, H., Higuchi, S., Sakamaki, T., Hart, J. A., Hart, T. B., … Furuichi, T. (2013). Genetic structure of wild bonobo populations: Diversity of mitochondrial DNA and geographical distribution. *PLoS ONE*, *8*, e59660. https://doi.org/10.1371/journal.pone.0059660

Kelly, A., Powis, S. H., Kerr, L. A., Mockridge, I., Elliott, T., Bastin, J., … Townsend, A. (1992). Assembly and function of the two ABC transporter proteins encoded in the human major histocompatibility complex. *Nature*, *355*, 641–644. https://doi.org/10.1038/355641a0

Kelly, A., & Trowsdale, J. (2019). Genetics of antigen processing and presentation. *Immunogenetics*, *71*, 161–170. https://doi.org/10.1007/s00251-018-1082-2

Khazand, M., Peiberg, C., Nagy, M., & Sauermann, U. (1999). Mhc-DQ-DRB haplotype analysis in the rhesus macaque: Evidence for a number of different haplotypes displaying a low allelic polymorphism. *Tissue Antigens*, *54*, 615–624. https://doi.org/10.1034/j.1399-0039.1999.540612.x

Kiepiela, P., Leslie, A. J., Honeyborne, I., Ramduth, D., Thobakgale, C., Chetty, S., … Goulder, P. J. (2004). Dominant influence of HLA-B in mediating the potential co-evolution of HIV and HLA. *Nature*, *432*, 769–775. https://doi.org/10.1038/nature03113

Knapp, L. A., Cadavid, L. F., & Watkins, D. I. (1998). The MHC-E locus is the most well conserved of all known primate class I histocompatibility genes. *The Journal of Immunology*, *160*, 189–196.

Kono, A., Brameier, M., Roos, C., Suzuki, S., Shigenari, A., Kametani, Y., … Shiina, T. (2014). Genomic sequence analysis of the MHC class I G/F segment in common marmoset (Callithrix jacchus). *The Journal of Immunology*, *192*, 3239–3246.

Kulski, J. K., Anzai, T., Shiina, T., & Inoko, H. (2004). Rhesus macaque class I duplicon structures, organization, and evolution within the alpha block of the major histocompatibility complex. *Molecular Biology and Evolution*, *21*, 2079–2091. https://doi.org/10.1093/molbev/msh216

Lawlor, D. A., Warren, E., Taylor, P., & Parham, P. (1991). Gorilla class I major histocompatibility complex alleles: Comparison to human and chimpanzee class I. *Journal of Experimental Medicine*, *174*, 1491–1509. https://doi.org/10.1084/jem.174.6.1491

Leddon, S. A., & Sant, A. J. (2010). Generation of MHC class II-peptide ligands for CD4 T-cell allorecognition of MHC class II molecules. *Curr Opin Organ Transplant*, *15*, 505–511. https://doi.org/10.1097/MOT.0b013e32833bfc5c

Lenormand, C., Bausinger, H., Gross, F., Signorino-Gelo, F., Koch, S., Peressin, M., … Tourne, S. (2012). HLA-DQA2 and HLA-DQB2 genes are specifically expressed in human Langerhans cells and encode a new HLA class II molecule. *The Journal of Immunology*, *188*, 3903–3911.

Lepin, E. J., Bastin, J. M., Allan, D. S., Roncador, G., Braud, V. M., Mason, D. Y., … O'Callaghan, C. A. (2000). Functional characterization of HLA-F and binding of HLA-F tetramers to ILT2 and ILT4 receptors. *European Journal of Immunology*, *30*, 3552–3561. https://doi.org/10.1002/1521-4141(200012)30:12<3552:AID-IMMU3552>3.0.CO;2-L

Li, Y., Ndjango, J. B., Learn, G. H., Ramirez, M. A., Keele, B. F., Bibollet-Ruche, F., … Hahn, B. H. (2012). Eastern chimpanzees, but not bonobos, represent a simian immunodeficiency virus reservoir. *Journal of Virology*, *86*, 10776–10791. https://doi.org/10.1128/JVI.01498-12

Locke, D. P., Hillier, L. D. W., Warren, W. C., Worley, K. C., Nazareth, L. V., Muzny, D. M., … Wilson, R. K. (2011). Comparative and demographic analysis of orang-utan genomes. *Nature*, *469*, 529–533. https://doi.org/10.1038/nature09687

Loffredo, J. T., Sidney, J., Bean, A. T., Beal, D. R., Bardet, W., Wahl, A., … Sette, A. (2009). Two MHC class I molecules associated with elite

control of immunodeficiency virus replication, Mamu-B*08 and HLA-B*2705, bind peptides with sequence similarity. *The Journal of Immunology*, *182*, 7763–7775. https://doi.org/10.4049/jimmunol.0900111

Lugo, J. S., & Cadavid, L. F. (2015). Patterns of MHC-G-Like and MHC-B diversification in new world monkeys. *PLoS ONE*, *10*, e0131343.

Maccari, G., Robinson, J., Ballingall, K., Guethlein, L. A., Grimholt, U., Kaufman, J., … Marsh, S. G. (2017). IPD-MHC 2.0: An improved inter-species database for the study of the major histocompatibility complex. *Nucleic Acids Research*, *45*, D860–D864.

Maibach, V., Hans, J. B., Hvilsom, C., Marques-Bonet, T., & Vigilant, L. (2017). MHC class I diversity in chimpanzees and bonobos. *Immunogenetics*, *69*, 661–676. https://doi.org/10.1007/s00251-017-0990-x

Marsh, S. G., Parham, P., & Barber, L. D. (2000). *The HLA Factsbook*. London, UK: Academic Press.

Mellars, P. (2006). Why did modern human populations disperse from Africa ca. 60,000 years ago? A new model. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 9381–9386. https://doi.org/10.1073/pnas.0510792103

Mothe, B. R., Southwood, S., Sidney, J., English, A. M., Wriston, A., Hoof, I., … Sette, A. (2013). Peptide-binding motifs associated with MHC molecules common in Chinese rhesus macaques are analogous to those of human HLA supertypes and include HLA-B27-like alleles. *Immunogenetics*, *65*, 371–386. https://doi.org/10.1007/s00251-013-0686-9

Nakamura, T., Shirouzu, T., Nakata, K., Yoshimura, N., & Ushigome, H. (2019) The role of major histocompatibility complex in organ transplantation- donor specific anti-major histocompatibility complex antibodies analysis goes to the next stage. *International Journal of Molecular Sciences*, *20*(18), 4544.

Nater, A., Mattle-Greminger, M. P., Nurcahyo, A., Nowak, M. G., de Manuel, M., Desai, T., … Krutzen, M. (2017). Morphometric, behavioral, and genomic evidence for a new orangutan species. *Current Biology*, *27*(3487–3498), e3410.

Otting, N., de Groot, N. G., & Bontrop, R. E. (2019). Limited MHC class II gene polymorphism in the West African chimpanzee is distributed maximally by haplotype diversity. *Immunogenetics*, *71*, 13–23. https://doi.org/10.1007/s00251-018-1080-4

Otting, N., de Groot, N., de Vos-Rouweler, A. J., Louwerse, A., Doxiadis, G. G., & Bontrop, R. E. (2012). Multilocus definition of MHC haplotypes in pedigreed cynomolgus macaques (Macaca fascicularis). *Immunogenetics*, *64*, 755–765. https://doi.org/10.1007/s00251-012-0632-2

Otting, N., van der Wiel, M. K., de Groot, N., de Vos-Rouweler, A. J., de Groot, N. G., Doxiadis, G. G., … Bontrop, R. E. (2017). The orthologs of HLA-DQ and -DP genes display abundant levels of variability in macaque species. *Immunogenetics*, *69*, 87–99. https://doi.org/10.1007/s00251-016-0954-6

Parham, P., Norman, P. J., Abi-Rached, L., & Guethlein, L. A. (2012). Human-specific evolution of killer cell immunoglobulin-like receptor recognition of major histocompatibility complex class I molecules. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *367*, 800–811. https://doi.org/10.1098/rstb.2011.0266

Perelman, P., Johnson, W. E., Roos, C., Seuanez, H. N., Horvath, J. E., Moreira, M. A., … Pecon-Slattery, J. (2011). A molecular phylogeny of living primates. *PLoS Genetics*, *7*, e1001342. https://doi.org/10.1371/journal.pgen.1001342

Pietra, G., Romagnani, C., Mazzarino, P., Falco, M., Millo, E., Moretta, A., … Mingari, M. C. (2003). HLA-E-restricted recognition of cytomegalovirus-derived peptides by human CD8+ cytolytic T lymphocytes. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 10896–10901. https://doi.org/10.1073/pnas.1834449100

Potkay, S. (1992). Diseases of the callitrichidae: A review. *Journal of Medical Primatology*, *21*, 189–236.

Prado-Martinez, J., Sudmant, P. H., Kidd, J. M., Li, H., Kelley, J. L., Lorente-Galdos, B., … Marques-Bonet, T. (2013). Great ape genetic diversity and population history. *Nature*, *499*, 471–475. https://doi.org/10.1038/nature12228

Prall, T. M., Graham, M. E., Karl, J. A., Wiseman, R. W., Ericsen, A. J., Raveendran, M., … O'Connor, D. H. (2017). Improved full-length killer cell immunoglobulin-like receptor transcript discovery in Mauritian cynomolgus macaques. *Immunogenetics*, *69*, 325–339. https://doi.org/10.1007/s00251-017-0977-7

Reed, J. S., Sidney, J., Piaskowski, S. M., Glidden, C. E., Leon, E. J., Burwitz, B. J., … Wilson, N. A. (2011). The role of MHC class I allele Mamu-A*07 during SIV(mac)239 infection. *Immunogenetics*, *63*, 789–807. https://doi.org/10.1007/s00251-011-0541-9

Robinson, J., Barker, D. J., Georgiou, X., Cooper, M. A., Flicek, P., & Marsh, S. G. E. (2020). IPD-IMGT/HLA database. *Nucleic Acids Research*, *48*, D948–D955.

Robinson, J., Halliwell, J. A., Hayhurst, J. D., Flicek, P., Parham, P., & Marsh, S. G. (2015). The IPD and IMGT/HLA database: Allele variant databases. *Nucleic Acids Research*, *43*, D423–431. https://doi.org/10.1093/nar/gku1161

Rosner, C., Kruse, P. H., Lubke, T., & Walter, L. (2010). Rhesus macaque MHC class I molecules show differential subcellular localizations. *Immunogenetics*, *62*, 149–158. https://doi.org/10.1007/s00251-010-0424-5

Salerno-Goncalves, R., Fernandez-Vina, M., Lewinsohn, D. M., & Sztein, M. B. (2004). Identification of a human HLA-E-restricted CD8+ T cell subset in volunteers immunized with Salmonella enterica serovar Typhi strain Ty21a typhoid vaccine. *The Journal of Immunology*, *173*, 5852–5862.

Scally, A., Dutheil, J. Y., Hillier, L. W., Jordan, G. E., Goodhead, I., Herrero, J., … Durbin, R. (2012). Insights into hominid evolution from the gorilla genome sequence. *Nature*, *483*, 169–175. https://doi.org/10.1038/nature10842

Sette, A., Sidney, J., Southwood, S., Moore, C., Berry, J., Dow, C., … Mothe, B. R. (2012). A shared MHC supertype motif emerges by convergent evolution in macaques and mice, but is totally absent in human MHC molecules. *Immunogenetics*, *64*, 421–434. https://doi.org/10.1007/s00251-011-0598-5

Shiina, T., Yamada, Y., Aarnink, A., Suzuki, S., Masuya, A., Ito, S., … Blancher, A. (2015). Discovery of novel MHC-class I alleles and haplotypes in Filipino cynomolgus macaques (Macaca fascicularis) by pyrosequencing and Sanger sequencing: Mafa-class I polymorphism. *Immunogenetics*, *67*, 563–578. https://doi.org/10.1007/s00251-015-0867-9

Shiroishi, M., Tsumoto, K., Amano, K., Shirakihara, Y., Colonna, M., Braud, V. M., … Maenaka, K. (2003). Human inhibitory receptors Ig-like transcript 2 (ILT2) and ILT4 compete with CD8 for MHC class I binding and bind preferentially to HLA-G. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 8856–8861. https://doi.org/10.1073/pnas.1431057100

Sidney, J., Peters, B., Frahm, N., Brander, C., & Sette, A. (2008). HLA class I supertypes: A revised and updated classification. *BMC Immunology*, *9*, 1. https://doi.org/10.1186/1471-2172-9-1

Slukvin, I. I., Grendell, R. L., Rao, D. S., Hughes, A. L., & Golos, T. G. (2006). Cloning of rhesus monkey LILRs. *Tissue Antigens*, *67*, 331–337. https://doi.org/10.1111/j.1399-0039.2006.00579.x

Soderstrom, K., Corliss, B., Lanier, L. L., & Phillips, J. H. (1997). CD94/NKG2 is the predominant inhibitory receptor involved in recognition of HLA-G by decidual and peripheral blood NK cells. *The Journal of Immunology*, *159*, 1072–1075.

Solomon, C., Southwood, S., Hoof, I., Rudersdorf, R., Peters, B., Sidney, J., … Mothe, B. R. (2010). The most common Chinese rhesus macaque MHC class I molecule shares peptide binding repertoire with

the HLA-B7 supertype. *Immunogenetics*, *62*, 451–464. https://doi.org/10.1007/s00251-010-0450-3

Southwood, S., Solomon, C., Hoof, I., Rudersdorf, R., Sidney, J., Peters, B., … Sette, A. (2011). Functional analysis of frequently expressed Chinese rhesus macaque MHC class I molecules Mamu-A1*02601 and Mamu-B*08301 reveals HLA-A2 and HLA-A3 supertypic specificities. *Immunogenetics*, *63*, 275–290. https://doi.org/10.1007/s00251-010-0502-8

Spies, T., Bresnahan, M., Bahram, S., Arnold, D., Blanck, G., Mellins, E., … DeMars, R. (1990). A gene in the human major histocompatibility complex class II region controlling the class I antigen presentation pathway. *Nature*, *348*, 744–747. https://doi.org/10.1038/348744a0

Steimle, V., Siegrist, C. A., Mottet, A., Lisowska-Grospierre, B., & Mach, B. (1994). Regulation of MHC class II expression by interferon-gamma mediated by the transactivator gene CIITA. *Science*, *265*, 106–109. https://doi.org/10.1126/science.8016643

t Hart, B. A., Bogers, W. M., Haanstra, K. G., Verreck, F. A., & Kocken, C. H. (2015). The translational value of non-human primates in preclinical research on infection and immunopathology. *European Journal of Pharmacology*, *759*, 69–83. https://doi.org/10.1016/j.ejphar.2015.03.023

Trowsdale, J. (2001). Genetic and functional relationships between MHC and NK receptor genes. *Immunity*, *15*, 363–374. https://doi.org/10.1016/S1074-7613(01)00197-2

Trowsdale, J., Hanson, I., Mockridge, I., Beck, S., Townsend, A., & Kelly, A. (1990). Sequences encoded in the class II region of the MHC related to the 'ABC' superfamily of transporters. *Nature*, *348*, 741–744. https://doi.org/10.1038/348741a0

Urvater, J. A., Otting, N., Loehrke, J. H., Rudersdorf, R., Slukvin, I. I., Piekarczyk, M. S., … Watkins, D. I. (2000). Mamu-I: A novel primate MHC class I B-related locus with unusually low variability. *The Journal of Immunology*, *164*, 1386–1398.

van der Wiel, M. K. H., Doxiadis, G. G. M., de Groot, N., Otting, N., de Groot, N. G., Poirier, N., … Bontrop, R. E. (2018). MHC class I diversity of olive baboons (Papio anubis) unravelled by next-generation sequencing. *Immunogenetics*, *70*, 439–448. https://doi.org/10.1007/s00251-018-1053-7

van der Wiel, M. K., Otting, N., de Groot, N. G., Doxiadis, G. G., & Bontrop, R. E. (2013). The repertoire of MHC class I genes in the common marmoset: Evidence for functional plasticity. *Immunogenetics*, *65*, 841–849. https://doi.org/10.1007/s00251-013-0732-7

van Ham, S. M., Tjin, E. P., Lillemeier, B. F., Gruneberg, U., van Meijgaarden, K. E., Pastoors, L., … Neefjes, J. (1997). HLA-DO is a negative modulator of HLA-DM-mediated MHC class II peptide loading. *Current Biology*, *7*, 950–957. https://doi.org/10.1016/S0960-9822(06)00414-3

Vierboom, M. P., Jonker, M., Bontrop, R. E., & t Hart B,, (2005). Modeling human arthritic diseases in nonhuman primates. *Arthritis Research & Therapy*, *7*, 145–154.

Watkins, D. I., Burton, D. R., Kallas, E. G., Moore, J. P., & Koff, W. C. (2008). Nonhuman primate models and the failure of the Merck HIV-1 vaccine in humans. *Nature Medicine*, *14*, 617–621. https://doi.org/10.1038/nm.f.1759

Watkins, D. I., Chen, Z. W., Garber, T. L., Hughes, A. L., & Letvin, N. L. (1991). Segmental exchange between MHC class I genes in a higher primate: Recombination in the gorilla between the ancestor of a human non-functional gene and an A locus gene. *Immunogenetics*, *34*, 185–191. https://doi.org/10.1007/BF00205822

Watkins, D. I., Chen, Z. W., Hughes, A. L., Evans, M. G., Tedder, T. F., & Letvin, N. L. (1990). Evolution of the MHC class I genes of a New World primate from ancestral homologues of human non-classical genes. *Nature*, *346*, 60–63. https://doi.org/10.1038/346060a0

Wiseman, R. W., Karl, J. A., Bimber, B. N., O'Leary, C. E., Lank, S. M., Tuscher, J. J., … O'Connor, D. H. (2009). Major histocompatibility complex genotyping with massively parallel pyrosequencing. *Nature Medicine*, *15*, 1322–1326. https://doi.org/10.1038/nm.2038

Wroblewski, E. E., Guethlein, L. A., Norman, P. J., Li, Y., Shaw, C. M., Han, A. S., … Parham, P. (2017). Bonobos Maintain Immune System Diversity with Three Functional Types of MHC-B. *The Journal of Immunology*, *198*, 3480–3493. https://doi.org/10.4049/jimmunol.1601955

Wroblewski, E. E., Norman, P. J., Guethlein, L. A., Rudicell, R. S., Ramirez, M. A., Li, Y., … Parham, P. (2015). Signature Patterns of MHC Diversity in Three Gombe Communities of Wild Chimpanzees Reflect Fitness in Reproduction and Immune Defense against SIVcpz. *PLoS Biology*, *13*, e1002144. https://doi.org/10.1371/journal.pbio.1002144

Wroblewski, E. E., Parham, P., & Guethlein, L. A. (2019). Two to Tango: Co-evolution of hominid natural killer cell receptors and MHC. *Frontiers in Immunology*, *10*, 177. https://doi.org/10.3389/fimmu.2019.00177

Wu, H. L., Wiseman, R. W., Hughes, C. M., Webb, G. M., Abdulhaqq, S. A., Bimber, B. N., … Sacha, J. B. (2018). The role of MHC-E in T cell immunity is conserved among humans, rhesus macaques, and cynomolgus macaques. *The Journal of Immunology*, *200*, 49–60. https://doi.org/10.4049/jimmunol.1700841

Yan, W. H., & Fan, L. A. (2005). Residues Met76 and Gln79 in HLA-G alpha1 domain involve in KIR2DL4 recognition. *Cell Research*, *15*, 176–182.

Zsurka, G., Kudina, T., Peeva, V., Hallmann, K., Elger, C. E., Khrapko, K., & Kunz, W. S. (2010). Distinct patterns of mitochondrial genome diversity in bonobos (Pan paniscus) and humans. *BMC Evolutionary Biology*, *10*, 270. https://doi.org/10.1186/1471-2148-10-270

How to cite this article: Heijmans CMC, de Groot NG, Bontrop RE. Comparative genetics of the major histocompatibility complex in humans and nonhuman primates. *Int J Immunogenet*. 2020;47:243–260. https://doi.org/10.1111/iji.12490