Reduced MIC Gene Repertoire Variation in West African Chimpanzees as Compared to Humans

Natasja G. de Groot,* Christian A. Garcia,† Ernst J. Verschoor,* Gaby G. M. Doxiadis,* Steven G. E. Marsh,† Nel Otting,* and Ronald E. Bontrop*

*Departments of Comparative Genetics and Refinement, and Virology, Biomedical Primate Research Centre, Rijswijk, The Netherlands; and †Anthony Nolan Research Institute and Royal Free and UCL School of Medicine, Royal Free Campus, London, United Kingdom

The human major histocompatibility complex class I chain-related (MIC) genes are members of a multicyclic family showing similarity to the classical HLA-A, HLA-B, and HLA-C genes. Only the MICA and MICB genes produce functional transcripts. In chimpanzees, however, only one MIC gene is expressed, showing an intermediate character, resulting from a deletion fusing the MICA and MICB gene segments together. The present population study illustrates that all chimpanzee haplotypes sampled possess the hybrid MICA/B gene. In contrast to the human situation this gene displays reduced allelic variation. The observed repertoire reduction of the chimpanzee MICA/B gene is in conformity with the severe repertoire condensation documented for Patr-B locus lineages, probably due to the close proximity of both genes.

Introduction

The major histocompatibility complex class I chain-related gene (MIC), previously also called PERB11, was first described in 1994 (Bahram et al. 1994; Leelayuwat et al. 1994). The gene is located in the major histocompatibility complex (MHC) region. The MHC, playing an important role in the immune defense against pathogens, is characterized by its extensive degree of polymorphism at the population level. Also, in the relatively small sample size of chimpanzees that have been analyzed so far, a high degree of Patr class I diversity, with regard to allele numbers, has been detected (Adams et al. 2000; de Groot et al. 2000). At first sight, this agrees with the finding that chimpanzees display more mitochondrial DNA (mtDNA) variation than humans do (Gagneux et al. 1999; Ingman et al. 2000), and similar findings have been reported for particular nuclear genes (Kaessmann, Wiebe, and Paabo 1999; Zhao et al. 2000). However, a recent publication shows that the variation in chimpanzees is not as high as a magnitude of four but more in the range of 1.5 compared to humans (Yu et al. 2003). A more detailed analysis of the MHC class I intron 2 sequences in chimpanzees showed that the MHC class I gene repertoire, with respect to the number of lineages, is severely reduced as compared to humans. This repertoire reduction is evident for Patr-A (McAdam et al. 1995) but is most prominent for the Patr-B locus lineages (de Groot et al. 2002).

Seven MIC genes are distinguished in the human genome. MICA and MICB produce functional transcripts, whereas MICC to MICG are pseudogenes (Bahram 2000). The MICA and MICB genes show a high degree of similarity to the classical MHC class I genes but are distinguished by their disparate organization of exons-introns. Moreover, they do not associate with β2-microglobulin (β2m), and their expression is not induced by type I/II interferons. Furthermore, the MICA and MICB genes are predominantly expressed on fibroblast and epithelial cells (Bahram 2000). A part of the MICA and MICB promoter region shows similarity to heat shock protein gene promoters, and upregulation of the MICA and MICB molecules after heat shock has been reported (Groh et al. 1998). In conclusion, MICA and MICB seem to play a role in the detection of cell stress and appear to react preferentially with the ligands Vδ1 γδ TCR and NKG2D to induce an immune response (Groh et al. 1998; Bauer et al. 1999; Gleimmer and Parham 2003). In chimpanzees only one functional MIC gene has been described (Steinle, Groh, and Spies 1998), and this gene appears to have an intermediate character as compared to human MICA and MICB genes (Cattley et al. 1999; Kulski et al. 2002). Studies on MIC gene polymorphism in chimpanzee populations are absent, and only one allele, Patr-MIC1, has been reported (Steinle, Groh, and Spies 1998). The human MICA and MICB genes show a considerable degree of polymorphism, and to date 54 MICA and 14 MICB alleles have been identified (Radosavljevic and Bahram 2003).

Compared to humans, chimpanzees have a severely reduced MHC class I gene repertoire caused by an ancient selective sweep (de Groot et al. 2002), and they appear to lack the equivalents of the HLA-DRBI*04 and HLA-DRBI*08 lineages (Bontrop et al. 1999). The present study was initiated to investigate whether the repertoire reduction, most prominent for the Patr-B locus lineages, is only restricted to the MHC class I and II genes or also extends to other genes located in the MHC region. For that reason we investigated the polymorphism at the chimpanzee MIC gene, which is located in the direct neighborhood of the Patr-B locus (Anzai et al. 2003). In humans, some of the MICA alleles and closely linked HLA-B alleles show a high degree of linkage disequilibrium (Bahram 2000). Here we report on MIC gene variation and linkage disequilibrium in a West African chimpanzee population together with data on chimpanzees of other subspecies.

Materials and Methods

Animals

The chimpanzee (Pan troglodytes) colony (approximately 100 individuals) at the Biomedical Primate Research Centre (BPRC) started with 35 founder animals
originating from Sierra Leone and belonging to the subspecies *Pan troglodytes verus* (West Africa). The animals are characterized at the molecular level for MHC class I and II gene polymorphisms (Bontrop et al. 1999; de Groot et al. 2000). Their offspring have been pedigreed based on segregation of Patr-A and Patr-B serotypes and molecularly defined *Patr* class I and II gene polymorphisms. Three animals of the *Pan troglodytes troglodytes* (Central Africa) and *Pan troglodytes schweinfurthii* (East Africa) subspecies have been included in this study. For the two bonobos (*Pan paniscus*) used in this study, the DNAs were analyzed with 12S primers to determine potential relationships (Kocher et al. 1989).

**mtDNA Analysis**

Genomic DNA (gDNA), obtained from Epstein-Barr virus-transformed B-cell lines, was used to amplify the mitochondrial D-loop (380 bp) sequences. To assign the subspecies, the nucleotide sequences were compared to published sequences (Morin et al. 1994; Gagneux et al. 1999). The polymerase chain reaction (PCR) mixture (50 μl) contained gDNA (50 ng), 1 μM of the primers (table 1), 1× PCR buffer + bovine serum albumin, 2 mM MgCl₂, 0.2 mM of each deoxyribonucleoside triphosphate (dNTP), and 2.5 units (U) *Taq* polymerase Gold (Applied Biosystems, Foster City, Calif.). A touchdown PCR consisting of the following cycles was run: 1 cycle of 15 min at 94°C, 2 cycles of 30 s at 94°C, 30 s at 63°C, 30 s at 72°C; after each two cycles the annealing temperature is decreased by 2°C until 55°C was reached, followed by 4 cycles of 30 s at 94°C, 30 s at 53°C, 30 s at 72°C, and 25 cycles of 30 s at 94°C, 30 s at 50°C, 30 s at 72°C, with a final extension of 5 min at 72°C. The PCR products were purified using the QIAquick Gel Extraction Kit (Qiagen, Hilden, Germany), and sequenced directly on an ABI 310 automatic sequencer using the ABI Prism dRhodamine Terminator Cycle sequencing Ready Reaction Kit (Applied Biosystems) to prepare the samples according to the manufacturer’s instructions. The products were sequenced from the 5' and 3' ends. Sequences reported in this publication have been deposited in the EMBL database (accession numbers AJ863489–AJ863508).

**MIC Gene Characterization by Direct Nucleotide Sequencing**

gDNA was used for the PCR amplification. Two independent overlapping PCR fragments were generated, using *MIC*-specific primers (table 1), covering the *MIC* gene from exon 2 to exon 5. This resulted in a 1,046-bp PCR fragment (fragment A), covering exon 2 (255 bp), intron 2 (273 bp), and exon 3 (270 bp), and a part of introns 1 (101 bp) and 3 (100 bp). The second PCR product was 1,297-bp long (fragment B), containing complete intron 3 (596 bp), exon 4 (270 bp), intron 4 (102 bp), and exon 5 (141 bp), and a part of exon 3 (129 bp) and intron 5 (13 bp). The PCR for fragment A (25 μl) contained gDNA (100 ng), 0.8 μM of the primers (table 1), 2.5–3 mM MgCl₂, 0.4 mM of each dNTP, and 5 U of *Taq* polymerase. A total of 33 cycles were run, each cycle consisting of 30 s at 95°C, 50 s at 61.3°C, and 30 s at 72°C with a final extension of 8 min at 72°C. PCR for fragment B (50 μl) contained gDNA (100 ng), 0.8 μM of the primers (table 1), 2.25–2.75 mM MgCl₂, 0.4 mM of each dNTP, and 5 U of *Taq* polymerase. A total of 28 cycles were run, each cycle consisting of 30 s at 95°C, 30 s at 58.5°C, and 40 s at 72°C with a final extension of 7 min at 72°C. The PCR products were purified, and sequenced directly on an ABI 3100 genetic analyzer (Applied Biosystems) using the PCR primers and specific internal sequencing primers (table 1). Cycle sequencing reactions were carried out with ABI Prism BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) using 0.2 μM primer, 1 μl BigDye terminator, and 5× sequencing dilution buffer (400 mM Tris-HCl, 10 mM MgCl₂) in a 10 μl reaction. The sequences were analyzed using the Sequence Navigator program (Applied Biosystems). At least two independent PCR reactions were performed to confirm the allele.

**MIC Allele Characterization by T/A-Cloning and Sequencing**

The PCR for fragment B was performed as described above with the exception that in the PCR program the final extension step is changed into 30 min at 72°C. For *MIC*
allele characterization the PCR products of fragment B were purified, ligated into the plasmid vector pTZ57R/T, and utilized in the transformation using the Ins T/A clone PCR product cloning Kit (Fermentas, St. Leon-Rot, Germany). Clones were isolated by the minipreparation protocol of Qiagen and sequenced as mentioned in the section above. Sequences reported in this publication have been deposited in the EMBL database (accession numbers AJ748822–AJ748831).

Phylogenetic Analysis

Neighbor-Joining (NJ) trees were constructed with the PAUP* program version 4.0b10 for Macintosh, using the method of Jukes-Cantor correction for multiple hits (Jukes 1969) for figure 1, and Kimura’s two-parameter model (Swofford 1992) for figure 7. Bootstrap values were based on 1,000 resamplings. The PAUP* program was also used to construct phylogenetic trees using the maximum likelihood method (full heuristic search and quartet puzzling). These trees gave topologies similar to the NJ trees.

Nomenclature

The Patr-MICA/B alleles received official designations. The first two digits identify the lineage, while the third and fourth digits reflect the order in which the alleles were found. The fifth digit reflects a mutation in the non-coding region. Sequences will be listed in the IMGT/MHC database (Robinson et al. 2003).

Results and Discussion

mtDNA and MIC Gene Analysis in Chimpanzees

From the 35 founder animals of the BPRC colony, 30 chimpanzees were selected for the present project.
Phylogenetic analysis of the mtDNA D-loop sequences shows that most of the founder animals are not related (fig. 1). Although identical mtDNA D-loop sequences were detected in some chimpanzees, these animals appear to possess different MHC haplotypes (fig. 2).

Fifty-three chimpanzees (30 founder animals and 23 offspring) were screened by RSCA for MIC gene–associated polymorphisms. Three different fragments, covering exons 2 and 3 of the gene, were detected. The nucleotide sequence corresponding to the 2B/3B fragment is identical to the earlier published Patr-MIC1 allele (Steinle, Groh, and Spies 1998), which is renamed Patr-MICA/B*01011. The 2A/3A and 2C/3B fragments correspond with the Patr-MICA/B*0102*0103 alleles, respectively. Several additional chimpanzees were analyzed by direct sequencing, resulting in the detection of three other alleles, which are designated Patr-MICA/B*0104*0105*0106 (figs. 3 and 4). The Patr-MICA/B*0104 and *0106 alleles are present in the subspecies P. t. troglodytes, whereas Patr-MICA/B*0105 is detected in P. t. schweinfurthii. All six alleles share an identical intron 2, reflecting their common ancestry.

In the classical MHC class I genes most polymorphism is confined to exons 2 and 3. In humans, however, MICA polymorphism is not exclusively restricted to these exons, but is also located in exon 4 (Fodil et al. 1996). Therefore the study was extended by sequencing intron 3 to exon 5, resulting in the definition of three other alleles, which are designated Patr-MICA/B*0104, *0105, and *0106 (figs. 3 and 4). The Patr-MICA/B*0104 and *0106 alleles are present in the subspecies P. t. troglodytes, whereas Patr-MICA/B*0105 is detected in P. t. schweinfurthii. All six alleles share an identical intron 2, reflecting their common ancestry.

In the classical MHC class I genes most polymorphism is confined to exons 2 and 3. In humans, however, MICA polymorphism is not exclusively restricted to these exons, but is also located in exon 4 (Fodil et al. 1996). Therefore the study was extended by sequencing intron 3 to exon 5, resulting in the definition of three other alleles, which are designated Patr-MICA/B*0104, *0105, and *0106 (figs. 3 and 4). The Patr-MICA/B*0104 and *0106 alleles are present in the subspecies P. t. troglodytes, whereas Patr-MICA/B*0105 is detected in P. t. schweinfurthii. All six alleles share an identical intron 2, reflecting their common ancestry.

In the classical MHC class I genes most polymorphism is confined to exons 2 and 3. In humans, however, MICA polymorphism is not exclusively restricted to these exons, but is also located in exon 4 (Fodil et al. 1996). Therefore the study was extended by sequencing intron 3 to exon 5, resulting in the definition of three other alleles, which are designated Patr-MICA/B*0104, *0105, and *0106 (figs. 3 and 4). The Patr-MICA/B*0104 and *0106 alleles are present in the subspecies P. t. troglodytes, whereas Patr-MICA/B*0105 is detected in P. t. schweinfurthii. All six alleles share an identical intron 2, reflecting their common ancestry.

In the classical MHC class I genes most polymorphism is confined to exons 2 and 3. In humans, however, MICA polymorphism is not exclusively restricted to these exons, but is also located in exon 4 (Fodil et al. 1996). Therefore the study was extended by sequencing intron 3 to exon 5, resulting in the definition of three other alleles, which are designated Patr-MICA/B*0104, *0105, and *0106 (figs. 3 and 4). The Patr-MICA/B*0104 and *0106 alleles are present in the subspecies P. t. troglodytes, whereas Patr-MICA/B*0105 is detected in P. t. schweinfurthii. All six alleles share an identical intron 2, reflecting their common ancestry.
**Fig. 3.**—Deduced amino acid sequences of the *Patr-MICA/B* alleles. Human *MICA*^*004* (X92841) is used as a reference, and human *MICB* (U65416) and *Mamu-MICA(1) and B(2)* (AC148666 and AC148679) are given for comparison. Identity to *MIC*^*004* is indicated by dashes, whereas amino acid replacements are depicted by the conventional one-letter code. Dots indicate a deletion. The alleles *Patr-MIC1* (AF055384) and *Patr-MIC1*^*02* (AF322858) were renamed *Patr-MICA/B*^*0101* and *Patr-MICA/B*^*0102*, respectively. The gray boxes indicate the part of the *Patr-MICA/B* gene that is more comparable to the human *MICB* gene, whereas exon 2 of the *Patr-MICA/B* gene is more related to human *MICA*. The open boxes in exon 5 indicate the alanine-repeat present in the human *MICA* and *Mamu-MICA(1)* gene. In humans this repeat can vary from 2 to 10 repeats per allele (Robinson et al. 2003).
the genomic organization of the rhesus macaque MHC was published, showing the presence of a MICA1 and MICA2 gene that are situated on the chromosome on locations comparable to those of the human MICA and MICA2 gene (Daza-Vamenta et al. 2004). Furthermore, Mamu-MICA1 possesses the characteristic GCT-repeat coding for alanine residues (fig. 3), although the alanine residues are interrupted by one valine. Thus, MICA1 seems to be the orthologue of the human MICA gene. In Mamu-MICA2 the repeat is absent, and, additionally, intron 3 shows features that are characteristic for MICA2 (fig. 6, gray boxes). Despite evidence that an ancestor of humans, great apes, and Old World monkeys possessed a MICA-like and MICA2-like gene tandem on a haplotype (fig. 5A), it is evident that these genes diversified considerably in humans versus rhesus macaques.

It is not known whether a MICA2-like gene is present in gorillas or orangutans. We therefore designed primers amplifying partial MICA2 intron 3 (nucleotide positions 235–513), including the characteristic insert (fig. 6). In orangutans we were able to amplify this sequence, indicating that at least a MICA2-like gene segment is present in this species (fig. 5A). However, the primers did not produce a product with gorilla samples. This could indicate that a MICA2-like gene is absent in gorillas, although the possibility that the primers are not working optimally cannot be excluded.

Exon 2 of the human MICA and MIB2 and the Patr-MICA/B nucleotide sequences were subjected to phylogenetic analysis together with the known gorilla, orangutan, and rhesus macaque MICA and MIB2 orthologues (fig. 7). The tree illustrates that this part of the Patr-MICA/B gene is distantly related to the human MICA gene but shows a reduced level of variation of one lineage versus four lineages, respectively. The second part of the Patr-MICA/B sequences, exons 3 to 5, showed a more intermediate character versus human MICA and MIB2 (data not shown). Comparison of the data shows that intron 3 of the Patr-MICA/B alleles possesses features more characteristic of the human MICA gene (fig. 6), and in addition exon 5 illustrates the more close genetic relation of the chimpanzee and human MICA sequences (fig. 3). The reported chimpanzee class I region is characterized by a 95-kb genomic deletion resulting in a Patr-MICA/B fusion product (fig. 5B) (Kulski et al. 2002; Anzai et al. 2003). The present communication shows that all chimpanzees analyzed so far possess haplotypes with the hybrid MICA/B gene. MICA polymorphism studies in humans resulted in the identification of 54 different alleles (Petersdorf et al. 1999; Visser et al. 1999; Yao et al. 1999; Bahram 2000; Robinson et al. 2001), whereas for MICA14 different alleles are detected (Bahram and Spies 1996; Ando et al. 1997; Pellet et al. 1997; Visser et al. 1998). In the 30 unrelated West African chimpanzees studied, only four MICA/B alleles were identified (fig. 4), of which only three encode slightly distinct proteins (fig. 3). All variation can be explained by point mutations. Likewise, in the two other chimpanzee subspecies studied, only hybrid MICA/B sequences are detected. Taken together, 10 Patr-MICA/B alleles were identified, among which 7 encode for distinct proteins. Thus, it seems that West African chimpanzees have only one functional copy of a MICA gene, which possesses only one lineage and limited allelic variation, and the same trend seems to be observed in chimpanzees of other subspecies. Analysis of the Patr-MICA/B gene introns 3 and 4 revealed limited allelic variation, five and two different sequences, respectively. In the 595 nucleotide bases of intron 3, only one (Patr-MICA/B*01012 and Patr-MICA/B*01014) or three (Patr-MICA/B*0105) nucleotide substitutions are observed (fig. 4). The existence of these few nucleotide substitutions indicates that the alleles are probably of relatively recent origin.

One question to be answered is: when did the 95-kb deletion resulting in a Patr-MICA/B fusion product take place? Most likely this deletion occurred after the human-chimpanzee split (fig. 5A). The presence of an equivalent in bonobos indicates that the deletion happened before the speciation of chimpanzee and bonobo approximately 2 MYA. Thus, the deletion took place in the interval of 2 to 5–6 MYA (fig. 5A). The alternative explanation, that the human genome experienced a 95-kb insertion generating the MICA and MIB2 genes, is highly unlikely. Such an assumption is also in disagreement with the fact that the existence of the MICA gene predates the speciation of humans, chimpanzees, gorillas, orangutans (Pellet et al. 1999), and rhesus macaques (fig. 5A) (Daza-Vamenta
et al. 2004). This would imply that all ancestral chimpanzee haplotypes with the original Patr-MICA and Patr-MICB genes have been subject to a strong negative selection because these genes are apparently absent in the contemporary population. Earlier we reported that both the MHC class I Patr-A and Patr-B loci have suffered a severe repertoire reduction with regard to lineages, as compared to the human population. The intron 2 analysis suggested that the selective sweep in the MHC region occurred approximately 2 to 3 MYA (de Groot et al. 2002). Due to the close vicinity of the Patr-B and Patr-MICA/B loci it is possible that the hybrid Patr-MICA/B gene was selected based on a piggyback effect.

In humans, four candidate genes are found within the 95-kb section that is deleted: namely two uncharacterized transcripts, 3.8-1.1 and P5-1 (class I-like transcript), and two pseudogenes, HCGIX-1 and HLA-X (Kulski et al. 2002; Anzai et al. 2003). Based on the knowledge that humans and chimpanzees shared a common ancestor, it is highly probable that equivalents of these genes were also present in chimpanzees before the deletion. However, because the function of the 3.8-1.1 and P5-1 transcripts is unknown, we cannot exclude the possibility that the deletion of these genes may have given a selective advantage to chimpanzee haplotypes with the hybrid Patr-MICA/B gene.

**Linkage Between the MHC-B Locus and the Human MICA/Patr-MICA/B Locus**

In humans, particular MICA alleles are strongly associated to particular HLA-B alleles. From an evolutionary point of view one could expect that particular Patr-MICA/B alleles also show an association with certain Patr-B alleles. Genomic mapping studies demonstrated that the Patr-MICA/B gene and the human MICA gene are
located 45.2 and 46.4 kb centromeric from the MHC-B locus, respectively. However, in the well-characterized BPRC chimpanzee population, specific association between particular Patr-MICA/B alleles and particular Patr-B alleles is not observed. The most frequently detected MIC allele, Patr-MICA/B*01011, is present in all subspecies. Furthermore, all the Patr-MICA/B alleles that are detected seem to belong to one lineage. Again, it is possible that the Patr-B lineages/alleles that survived the ancient selective sweep were all linked to the frequently detected Patr-MICA/B*01011 allele and that the contemporary limited allelic variation seen in the Patr-MICA/B locus was generated after the selective sweep. Support for this observation is found in the Patr-MICA/B intron 3 sequences (fig. 4), where only a few nucleotide substitutions distinguish the different alleles. This most probably reflects their more recent origin.

Could Patr-MICA/B Contribute to AIDS Resistance in Chimpanzees?

Chimpanzees can be naturally infected with Simian immunodeficiency virus from chimpanzees (SIVcpz) but are also susceptible to infection with Human immunodeficiency virus type 1 (HIV-1). Although natural SIVcpz infections in West African chimpanzees have never been observed, the animals are susceptible to HIV-1 infection in captivity (Rutjens et al. 2003). In contrast to humans, chimpanzees normally do not develop symptoms of acquired immunodeficiency syndrome (AIDS). We have put forward the hypothesis that in the past chimpanzees may have been decimated by an AIDS-like pandemic caused by an HIV-1/SIVcpz-like retrovirus and that the contemporary population represents the offspring of the survivors (de Groot et al. 2002). In this respect, the contemporary chimpanzee population may have been enriched for resistance genes, and a candidate group that was identified is the group of the MHC molecules, which play an important role in controlling infections.

Chimpanzees are often described as herbivores, but they also hunt and consume other nonhuman primate species (Stanford et al. 1994). As most of these Old World monkeys have natural SIV infections, chimpanzees may have become infected through preying on infected monkeys. Probably chimpanzees have been infected multiple times and by various SIV-like strains (Courgnaud et al. 2002; Bailes et al. 2003). To date little is known about the transmission of SIVcpz between different chimpanzees. The initial infections with HIV-1/SIVcpz-like viruses in humans probably happened through blood contact during the hunting of infected chimpanzees. The routes of HIV-1 infection in humans are now known to be via intimate sexual contact, contaminated blood or blood products, or by transmission from mother to child (Levy, Scott, and Mackewicz 2003). Nonetheless, the intestine may be the major site for HIV replication and depletion of CD4 T cells (Veazey and Lackner 2004). In this perspective, it is possible that the hybrid Patr-MICA/B gene is highly efficient in detecting stress mediated by infection, and as such may induce efficient natural killer (NK) cell–mediated killing.

The human MICA and probably also the closely related MICB molecules are ligands for the NKG2D receptor, which is expressed on NK cells, CD8 T cells, and CD8 T cells. After cellular stress, triggered for instance by a viral infection or malignant transformation, MIC is upregulated and may provoke an immune response (Bauer et al. 1999; Gleimer and Parham 2003). Recent work, for instance, showed that the activating KIR gene KIR3DS1 is associated with a delay in progression to AIDS in HIV-1–infected individuals (Martin et al. 2002). The chimpanzee MICA/B molecule is able to recognize human Vα17γδ T cells specific for MICA and MICB, suggesting a conserved recognition site (Steinle, Groh, and Spies 1998). Indeed, also the NKG2D receptor shows a high
degree of similarity, approximately 98.9%, between humans and chimpanzees (Shum et al. 2002). Based upon these observations and the knowledge that humans and chimpanzees are closely related, a similar kind of immune response as described in humans is plausible.

The possible role of MIC-elicited anti-HIV-1/SIVcpz NK effector responses remains to be proved, and subsequent studies will be required to elucidate the functional significance of the *Patr-MICA/B* gene in virus infections.

**Acknowledgments**

The authors wish to thank D. Devine and H. van Westbroek for expert assistance, J. Heeney for discussion, and
S. Langehuizen for technical assistance. This study was financed in part by the European Union Project, IMGT-QLG2-2000-01287.

Literature Cited


tatic interaction between KIR3DS1 and HLA-B delays the progression to AIDS. Nat. Genet. 31:429–434.


David Goldstein, Associate Editor

Accepted February 28, 2005