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THE INFLUENCE OF *HLA* GENOTYPE ON AIDS*

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■ **Abstract** Genetic resistance to infectious diseases is likely to involve a complex array of immune-response and other genes with variants that impose subtle but significant consequences on gene expression or protein function. We have gained considerable insight into the genetic determinants of HIV-1 disease, and the *HLA* class I genes appear to be highly influential in this regard. Numerous reports have identified a role for *HLA* genotype in AIDS outcomes, implicating many *HLA* alleles in various aspects of HIV disease. Here we review the *HLA* associations with progression to AIDS that have been consistently affirmed and discuss the underlying mechanisms behind some of these associations based on functional studies of immune cell recognition.

INTRODUCTION

HIV/AIDS is a leading cause of infectious disease mortality worldwide. The current epidemic has killed over 21 million people (http://www.who.int/infectious-disease-report). At its current rate of approximately 3 million deaths per year, HIV will soon have caused more deaths than any other disease epidemic in recorded history. The virus is transmitted at an astounding rate in developing countries, accounting for 92% of the 5.3 million new cases of HIV infection worldwide. These statistics stimulated intensive research conducted over the past two decades to understand HIV pathogenesis in order to control infection and disease progression. The fruits of these efforts have not yet conquered the spread and severity of disease, particularly in underdeveloped countries, but we have learned more about this virus and its interactions with host cells than perhaps any other pathogen, strengthening our potential to devise intelligent, efficacious regimens for controlling the virus.

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As is the case for all infectious diseases, the level of resistance to HIV among exposed individuals is a function of the genetic variability of the pathogen, environment, and host. The exceedingly high mutation rate of HIV-1 (1–3) is a primary factor in the ability of the virus to ultimately escape elimination by an acquired immune response (4) and greatly complicates studies of viral isolate effects on disease pathogenesis. The variability in the viral genome is clearly demonstrated in the SIV/macaque model (5, 6), which enables infection with a single isolate of SIV in a controlled setting. These studies have indicated the plasticity of the virus in its ability to subvert host immune control. Immune avoidance and HIV's capacity to safely sequester itself from powerful antiretroviral therapy are profound survival mechanisms for this virus.

Defining host genetic factors that influence the response to HIV provides the means for predicting rates of disease progression and also suggests modes of pathogenesis that can lead to the development of therapeutics. A growing list of host genetic effects on HIV disease has been accumulating over the past several years (7–10), all of which were identified using a candidate gene approach. For the most part, genetic polymorphisms associated with AIDS progression or specific disease outcomes have involved genes encoding receptors for viral entry into cells and molecules that participate in innate or acquired immune responses. Although the influence of individual loci on AIDS progression tends to be weak in most cases, their cumulative effects appear quite substantial (7, 10). Among the dozen or so genetic effects of AIDS progression that have been substantiated in multiple study cohorts, the *HLA* class I loci clearly have the strongest effects on HIV disease progression identified to date. These epidemic influences can be interpreted in a functional context that affirms the importance of cytotoxic T cell responses in controlling HIV. Here we review the genetic effects of *HLA* class I and II loci on HIV disease, in the context of functional data when possible.

HLA AND DISEASE

The human major histocompatibility complex (MHC) maps to the short arm of chromosome 6 and contains the most polymorphic loci in humans, the *HLA* class I and class II genes (11, 11a). *HLA* gene products are fundamental to acquired immune responses. The classical class I loci, *HLA-A*, *-B*, and *-C*, encode molecules that bind antigenic epitopes usually derived from intracellular pathogens and present them to $CD8^+$ T cells, thereby initiating a cytotoxic T cell response. The classical class II loci, *HLA-DR*, *-DQ*, and *-DP*, specify molecules that primarily bind peptides of extracellular origin and present them to $CD4^+$ T cells, resulting in cytokine production and T cell help in antibody production. The extensive allelic polymorphism in HLA molecules is concentrated primarily among amino acid positions that determine specificity for foreign peptide presented by HLA cell surface molecules to T cell receptors (12, 13). The extraordinary diversity at these peptide binding residues of the HLA molecules is believed to be maintained through

natural selection by infectious disease morbidity and mortality (14, 15), and it ensures that, as a species, we are capable of resisting a wide variety of pathogens. Three models have been proposed to explain maintenance of *HLA* polymorphism: (*a*) balancing selection, where alleles that confer resistance to one disease confer susceptibility to another; (*b*) heterozygote advantage, where an increasing number of unique HLA types increases the breadth of peptide recognition and immune defense against infectious organisms (16); and (*c*) frequency-dependent selection, where a pathogen has evolved to escape an efficient immune response mediated by common alleles in the population but remains susceptible to responses mediated by low-frequency alleles. In addition, new selectively neutral or near-neutral variants can be maintained by hitchhiking effects of adjacent selected sites by opportunistic linkage association. Each of these mechanisms has probably been operative under various historic circumstances.

The MHC contains about 128 expressed genes, 40% of which encode products that function in the immune response (17). Polymorphisms have been identified in many of the genes, although except for the classical class I and II loci, few data support any functional significance for most of these variants. Common variants of the human antigen transporter proteins, the products of *TAP1* and *TAP2* genes, are not associated with any apparent alteration in function (18). Thus, putative associations between AIDS and human *TAP* variants are probably due to linkage disequilibrium with neighboring disease loci (19). By contrast, specific variants of rat *TAP* genes do affect the type of peptide transported into the endoplasmic reticulum by the TAP molecules (20). Considering the large number of functionally related loci mapping within the MHC and the strength of linkage disequilibrium among these loci (21, 22), it is often difficult to conclusively identify a specific disease locus within the MHC using genetic association studies in the absence of supporting functional data.

Over 100 diseases have been associated with the *HLA* loci, many of which are autoimmune in nature (23) and virtually all of which are multifactorial. *HLA* associations with infectious diseases have been difficult to identify, perhaps because a more complex array of antigenic epitopes is involved in infectious disease pathogenesis. Conclusive association studies regarding the influence of *HLA* on infectious disease require large samples, proper ethnic-background stratification, accurate clinical information, and use of models that consider other known genetic effects on the disease. Fulfilling these criteria completely is often difficult; numerous allelic associations with infection and disease outcomes have yet to be confirmed. Nevertheless, a number of convincing *HLA* class I and class II associations with infectious diseases have been identified (24). The protective effect of *HLA-B*53* against severe malaria in West Africa is particularly notable and may be responsible for the high frequency of *B*53* in this region (25). Other consistent *HLA* associations with infectious disease include susceptibility conferred by HLA-DR2 antigens in mycobacterial diseases (26, 27), immunological clearance of hepatitis C virus conferred by *DQB1*0301* (28–30), and clearance of hepatitis B virus among individuals with *DRB1*1302* (31, 32).

HIV/AIDS has been scrutinized extensively for effects conferred by *HLA*. *HLA* associations with HIV disease may be particularly apparent upon investigation, since the epidemic is recent and has not had time to significantly diminish frequencies of deleterious *HLA* alleles (19). Over 50 publications have described genetic associations between *HLA* and various aspects of HIV infection, but many relied on small samples and their findings were not confirmed in subsequent studies. Many of these studies have been thoroughly reviewed (33–35). The remainder of this article describes the most consistent *HLA* associations with HIV disease and functional data supporting observed genetic effects.

CLASS I HETEROZYGOTE ADVANTAGE AGAINST HIV DISEASE PROGRESSION

The hypothesis of overdominant selection (heterozygote advantage) proposes that individuals heterozygous at the *HLA* loci present a greater variety of antigenic peptides to T cells than do homozygotes, resulting in a more productive immune response to an array of pathogens (36, 37). Because of the extensive polymorphism, fairly even distribution of alleles at most of these loci (14, 15), and low allele frequencies, few individuals are homozygous at more than one locus. Detection of overdominant selection at the *HLA* loci would therefore require particularly large numbers of subjects, and the analysis would have to take into account other *HLA* effects (i.e., allelic, haplotypic, or genotypic) that could mask the influence of zygosity.

Using a cohort of 498 HIV-1–infected individuals with known dates of seroconversion, we tested the hypothesis that maximum diversity in the repertoire of antigen-presenting molecules is advantageous in delaying progression of AIDS after HIV infection (38). The results demonstrated a highly significant association of *HLA* class I homozygosity with rapid progression to AIDS in both Caucasians and African Americans. All three class I loci contributed independently to the association, and the effect was most pronounced in individuals who were homozygous at two or three loci. A more recent analysis of 1060 individuals from the same AIDS cohort studies confirmed the effects of homozygosity at one, two, and three loci on AIDS progression (Figure 1). Similar results were observed for homozygosity at *HLA-A* and *HLA-B* in 140 Dutch homosexual men and 202 Rwandan heterosexual women infected with HIV-1 (39). A stronger association between homozygosity and disease progression was observed at the *HLA-B* locus in the Amsterdam cohort and at the *HLA-A* locus in the Rwandan samples, and no effect was observed for homozygosity at the *HLA-C* locus in either of these cohorts.

One explanation for the effect of zygosity on AIDS progression is that heterozygotes can present a broader range of HIV-1 peptides, thereby prolonging the time it takes for an escape mutant to arise. Conclusive data that support viral immune escape from cytotoxic T lymphocyte (CTL) responses have been generated using the rhesus monkey model (5, 6), lending indirect support for an interpretation that implicates heterozygote advantage among individuals infected with HIV (38).

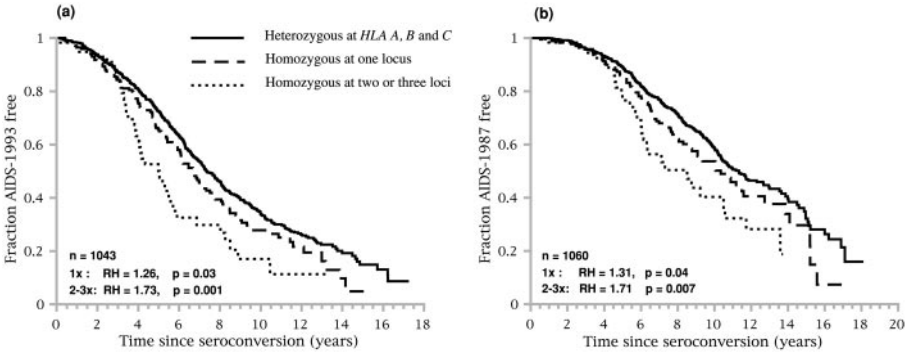

Figure 1 Association between homozygosity at one or more *HLA* class I loci and progression to the outcomes (*a*) AIDS in 1987 and (*b*) AIDS in 1993. Seroconverters from all ethnic groups (see Reference 38 for cohorts used) were used in the Kaplan Meier and Cox proportional hazards model (38). Relative hazards (RH) and the corresponding *p* values calculated by the Cox model are given for the singly and multiply homozygous groups compared with the completely heterozygous group. Racial groups were combined because there is no a priori reason to expect that a zygosity effect would vary across ethnic group.

However, other explanations for these results should also be considered, particularly in light of HIV-1's extremely rapid mutation rate (1–3). In this regard, frequency-dependent selection, where pathogens evolve under selection pressure from common *HLA* types to avoid a protective immune response conferred by these types (40, 41), could potentially explain the susceptibility effect of class I homozygosity. The model would predict that anyone who has two common alleles at one or more class I loci would be at greater risk for disease progression than individuals who have at least one infrequent allele at these loci. Since all *HLA* class I homozygotes necessarily involve the most common alleles in the study population, HIV pathogenesis would be enhanced in *HLA* homozygotes. If indeed frequency-dependent selection is operating in HIV pathogenesis, then a positive correlation should exist between susceptibility and number of common alleles at the class I loci per individual, and this effect should be stronger than that of *HLA* homozygosity.

ALLELIC EFFECTS OF *HLA* CLASS I ON AIDS PROGRESSION

Identifying genetic associations with HIV disease, particularly with loci as diverse as *HLA*, is complicated by extreme heterogeneity in the clinical course of AIDS progression, as well as in the differential incidence of HIV-1 infection among exposed individuals in different risk groups (42–46). Nevertheless, data replicated in independent cohort studies have implicated involvement of certain class I alleles in protection/susceptibility to AIDS progression (Table 1). These include a delay in AIDS progression associated with *HLA-B*27* and *B*57* (19, 47–50) (Figure 2) and an acceleration of AIDS onset conferred by *B*35* (48, 51–54). Studies of CTL

TABLE 1 Consistent *HLA* associations with HIV-1 disease

HLA genotype	Model	Frequency		Epidemiological effect	Possible functional explanation	Citations	
		Caucasians	African-Americans			Genetic	Functional
Class I homozygosity						38, 39	
One locus	—	16.9%	14%	Rapid progression	Narrow range of HIV-1 peptides are presented to CTL; immune escape occurs rapidly		
Two or three loci	—	5.5%	4.6%				
*HLA-B*27*	Dominant	5.1%	0.72%	Slow progression	Presents a conserved immunodominant epitope that is under structural constraint	19, 48, 49, 50	66, 67, 71, 72
*HLA-B*57*	Dominant	3.9%	6.1%	Slow progression	Broad cross-reactivity against HIV peptide variants	19, 29, 40, 45, 47, 48, 49, 54, 58	47, 59, 60, 61, 62
*HLA-B*35*	Codominant	7.7%	7.7%	Rapid progression*	Unknown	38, 48, 51, 52, 53	
HLA Class I mismatching in HIV transmission	—	—	—	Protection from infection	Allogenic immune response against HIV and donor cells	83, 84, 85, 86	

*A recent study (40) indicates that only a subset of *B*35* alleles (*B*3502, *3503, *3504*) associate with rapid AIDS progression.

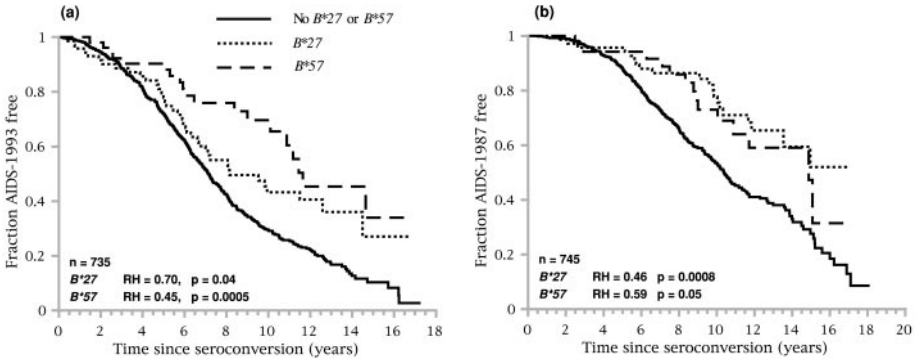

Figure 2 *HLA-B*27* and *B*57* protection against progression to (*a*) AIDS in 1993 and (*b*) AIDS in 1987 among Caucasian patients. Relative hazards (RH) and *p* values are given for *B*27* and *B*57* compared with genotypes negative for these alleles.

activity restricted by some of these HLA-B molecules have begun to provide the functional basis for several of the observed genetic effects (see below).

Although less consistently, and sometimes only in the presence of alleles at other MHC loci, studies have suggested that *HLA-B*51* and *-B*08* alleles also influence resistance and susceptibility, respectively, to disease progression (33, 34). Susceptibility conferred by *HLA-B*08* may explain previous reports of rapid progression to AIDS among individuals with the haplotype *HLA-A1-Cw7-B8-DR3-DQ2*, which is reknowned for its association with multiple autoimmune diseases (23).

All HLA-B molecules express one of two mutually exclusive serological epitopes termed Bw4 and Bw6, which are distinguished by variable amino acids within the motif spanning amino acid positions 77–83 (55). Most *HLA-B* alleles identified as having protective effects (*HLA-B*27*, *B*57*) carry the Bw4 specificity, whereas alleles associated with susceptibility (*HLA-B*35*, *B*08*) tend to have the Bw6 specificity. A recent report has suggested that protection against AIDS progression characterizes the Bw4 group of alleles as a whole when any two copies of Bw4 are present (56), although alternative epidemiological and mechanistic interpretations for these findings are possible (35). Nevertheless, the Bw4 association raises the intriguing possibility that natural killer cells are involved in regulating AIDS progression, since HLA-B molecules with the Bw4 motif not only present specific peptides to T cells but also serve as ligands for one of the natural killer cell receptors, KIR3DL1 (57).

*HLA-B*57*

Among the protective *HLA* effects identified to date, one of the most consistent genetic epidemiological associations has been with *HLA-B*57* (19, 35, 47, 48, 54, 58). Figure 2 illustrates a recent survival analysis of *HLA-B*57* and *B*27* in our AIDS cohorts. Recent studies have addressed the functional significance of the *B*57*

genetic association with long-term nonprogression to AIDS, and although no mechanism has been compellingly demonstrated, several interesting characteristics of this molecule have been reported. CTL responses restricted by B57 molecules target multiple HIV-1 peptides, with predominant responses observed against gag and reverse transcriptase motifs (59, 60). The Caucasian B5701 and the closely related African B5703 molecules both exhibit broad cross-reactivity against common and rare variants of a dominant gag epitope (61). Strong B57-restricted CTL responses can also occur against overlapping peptides of different length (62), further suggesting B57 plasticity in peptide binding. The broad peptide recognition specificity of B57 may enhance its AIDS-protective nature, although cross-reactivity against HIV peptide variants has been shown for other HLA types as well (63–65).

Dominant HIV-specific CTL responses among long-term nonprogressors who carry *B*57* primarily involve CTL epitopes restricted by HLA-B57 rather than epitopes restricted by other HLA types (60). Similarly, a protective effect of B*57-restricted responses was observed in a study comparing nonprogressors and rapid progressors to AIDS among subjects carrying B*57 (47). $CD8^+$ T cell responses of slow progressors were directed primarily toward B*57-restricted gag peptides, whereas B*57-positive patients who progressed to AIDS rapidly displayed a considerably broader response to gag peptides (47). Taken together, these studies suggest that viral escape from a B*57-restricted CTL response may be difficult, extending the B*57 carrier's resistance to the deadly march of HIV-1.

*HLA-B*27*

HLA-B27–restricted CTL responses to the HIV peptides recognized by these HLA molecules have been studied thoroughly, providing a plausible explanation for the observed protective epidemiological effect of *B*27*. An immunodominant response to a conserved HIV-1 epitope in p24 gag occurs in patients who carry HLA-B27 (66, 67), and this HLA-peptide complex is stabilized by the interaction between an arginine residue at position 2 of the HIV-1 peptide (position 264 of gag) and the B pocket of the B27 molecule (67–69). A viral gag amino acid substitution from arginine (R) to lysine (K) or glycine (G) at this same position results in a peptide that binds poorly to B27 (66, 70). This mutation correlates with a faster descent to AIDS in B27-positive individuals (66, 71), indicating that it may enable viral escape from B27-restricted CTLs. Evidence suggests that additional, compensatory mutations in the gag protein may be required in order for the virus to maintain replication fitness (71). The additional neighboring mutations may not compensate completely for the cost of R264K or R264G substitutions to viral fitness, however, since after the loss of the CTL response to the epitope and in the presence of high viral load, reversion to wild type occurs. The correlation between mutational viral escape from B27-restricted CTL responses and disease progression was also reported in a mother-infant transmission study (72). B27-positive mothers infected with HIV escape mutants involving the gag epitope transmitted these variants to their infants perinatally, resulting in the failure of the infected infants to contain HIV replication. Overall, the data indicate that the observed protective genetic effect

of B27 is due to its recognition of an HIV-1 gag epitope that is under structural restraint to remain intact and demonstrate the strong selection pressure certain HLA molecules can exert on the HIV mutational immune escape.

Individuals with *HLA-B*27* and *-B*57* also appear to respond more robustly to vaccines against HIV-1. CTL reactivity to ALVAC-HIV recombinant canarypox vaccines among a group of 291 HIV-1–negative subjects was more pronounced among individuals with *B*27* or *B*57* than among those with other *HLA* types (73). Whether this extends to protection against infection in the face of HIV exposure remains to be determined.

HLA-B 35*

*HLA-B*35*, which is almost always found in haplotypic association with *Cw*04*, is the allotype most consistently implicated in susceptibility to AIDS progression (38, 51–53). Analysis of 474 seroconverters for *HLA* class I allelic effects revealed only two alleles, *B*35* and *Cw*04*, among 63 assessed, that showed highly significant association with disease progression in Caucasians ($n = 330$) but not African-Americans ($n = 144$) (38). The difference observed between the two ethnic groups raised the question of whether *B*35*, *Cw*04*, or some other locus in linkage disequilibrium with these alleles accounts for accelerated AIDS progression. A subsequent study of 559 Caucasians and 210 African-Americans provided evidence that the operative locus was indeed *HLA-B* (48). In this study, *B*35* subtypes were divided into two groups according to peptide-binding specificity: (*a*) the *HLA-B*35-PY* group, composed of two closely related *HLA-B*35* alleles (including the most common, *B*3501*), which bind epitopes with proline in position 2 and tyrosine in position 9 (74, 75); and (*b*) the more broadly reactive *B*35-Px* group, which also binds epitopes with proline in position 2 but accepts several amino acids other than tyrosine in position 9. The data showed that accelerated AIDS progression among *B*35*-positive individuals was completely attributable to the *B*35-Px* alleles (Figure 3). The demonstration that the *B*35* susceptibility effect is partitioned exclusively and specifically according to peptide recognition (i.e., x or Y in position 9 of viral peptide) offers compelling evidence that *B*35* itself confers rapid progression to AIDS (48).

The dichotomy of B35-Px versus B35-PY peptide recognition and AIDS survival outcome would also explain the absence of a *B*35* association with rapid progression in African-Americans (Figure 3), since *B*3501*, the principal *B*35* allele present in this ethnic group, belongs to the *B*35-PY* group, which had no effect on AIDS progression. Furthermore, a *Cw*04* association reported previously in both Caucasians and African-Americans (38) is probably due to its linkage disequilibrium with *B*35-Px* alleles, since the pace of AIDS progression in patients with *Cw*04* but without *B*35-Px* subtype alleles is indistinguishable from that in patients without *Cw*04*.

A possible explanation for rapid AIDS progression among individuals with *B*35-Px* is that these alleles do not bind HIV peptides and fail to mediate a protective response in HIV-infected individuals. That is, *B*35-Px* would be equivalent to

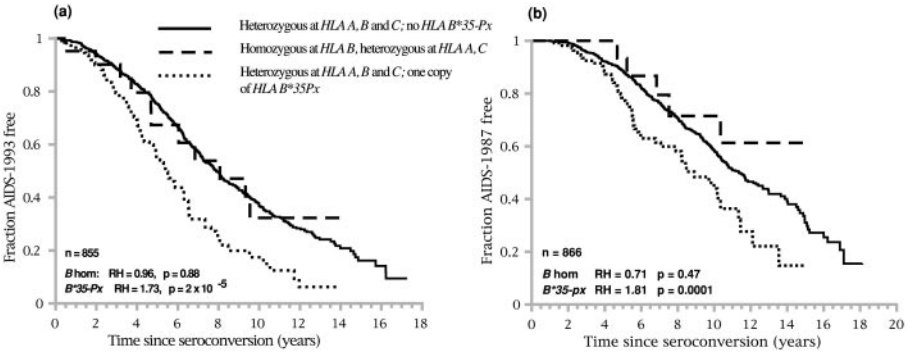

Figure 4 Susceptibility effect of *HLA-B*35-Px* relative to *HLA-B* homozygosity on progression to (*a*) AIDS-1987 and (*b*) AIDS-1993 among Caucasian patients. Relative hazards (RH) and *p* values are given for patients with one copy of *B*35-Px* (red curve), and homozygotes for the *HLA-B* locus only, relative to all other patients.

an *HLA-B* null allele. If this were so, then heterozygotes for *B*35-Px* would be functional hemizygotes and thus equivalent to homozygotes for any allele of the *HLA-B* locus. However, the rapidity of AIDS progression among *B*35-Px* heterozygotes is far greater than that observed in *HLA-B* homozygotes (Figure 4). Thus, we conclude that *B*35-Px* alleles exert an actively negative effect in AIDS pathogenesis.

The *B*35* analysis indicates that a single amino acid change in HLA molecules has a substantial effect on the progression to AIDS. The B3501 (PY) and B3503 (Px) molecules differ by a single amino acid at position 116 (Figure 3*c*,*d*), which forms the floor of the peptide-anchoring F pocket, determines the size of the peptide carboxy-terminal residue, and directly interacts with residue P9 of the bound peptide (76–78). Variation at this position is critical not only in determining peptide preference but also in facilitating interaction between HLA class I and the peptide-loading machinery in the endoplasmic reticulum for optimizing the peptide repertoire (79–81). Substitutions at position 116 also have been associated with an increased risk for transplant-related death (82), highlighting the clinical importance of amino acid variation at this site. The different consequences of B3501 (PY) and B3503 (Px) in terms of AIDS progression emphasize the significance of amino acid differences at position 116. However, other amino acid differences between the *B*35-Px* and *-PY* groups also appear to distinguish the groups functionally, since B5301, a member of the B35-Px group, is identical to B3501 (-PY group) at position 116.

INFLUENCE OF *HLA* ON RESISTANCE TO HIV INFECTION

The influence of *HLA* loci on resistance to HIV infection has been difficult to assess, since HIV exposure is very difficult to quantify precisely. Still, an increasing amount of genetic data has consistently indicated a protective role for *HLA* in

HIV transmission and infection (83–86). In a mother-infant study from Nairobi, Kenya, a progressive increase in the risk of perinatal HIV-1 transmission was observed for each additional concordant *HLA* class I allele transmitted to the offspring (83). An Edinburgh study of heterosexual transmission found similar results (84). These studies suggest that allogeneic immune responses may be protective against HIV transmission in a dose-dependent manner. However, no protection of mother-infant *HLA* discordance was observed among perinatally uninfected children who subsequently became infected from breastfeeding (83), suggesting that HLA-mediated responses may not be as effective against HIV challenge through the gastrointestinal mucosa.

Functional groupings of HLA molecules, known as supertypes, have been proposed based on similarity in structure, peptide-binding motif, epitope presentation, and evolutionary affinity of class I molecules (87–89). The A2/6802 supertype, composed of *A*0202*, *A*0205*, *A*0214*, and *A*6802*, was shown to be significantly associated with decreased frequency of HIV-1 seroconversion among a cohort of highly HIV-exposed prostitutes in Nairobi (86). This same set of supertype alleles (along with the *A*0201* allele, which was not significant in the sex workers study) conferred decreased perinatal HIV infection risk in the Nairobi mother-infant cohort, a subset of which showed the protective effect of HLA discordance between mother and child described above (85). These studies indicate that HLA may be involved in resistance to HIV transmission, and the possibility of a role for differential cell-mediated immune response in this resistance is tantalizing.

Functional analyses of $CD8^+$ T cell responses in individuals resistant to HIV-1 infection complement genetic studies that indicate protective effects of *HLA* class I loci in clearing the virus. HIV-specific CTL responses have been identified in a group of seronegative prostitutes from the Gambia (90), responses that persist for several years of follow-up. More recently, highly exposed seronegative prostitutes from Nairobi were shown to exhibit CTL responses to multiple conserved HIV epitopes, some of which are presented by HLA molecules associated with resistance to infection in this group of women (91). HIV-specific mucosal CTL responses were stronger in the seronegative Nairobi prostitutes than in HIV-infected donors (92), suggesting that CTL activity in the genital mucosa may play a key role in protection against heterosexual HIV-1 transmission. Consistent antigenic exposure appears to be necessary in order to maintain an effective HIV-specific CTL response (93).

HLA CLASS II AND PROGRESSION TO AIDS

Genetic epidemiological associations between HIV disease and *HLA* class II loci have not been as strong as those observed for class I, suggesting that cell-mediated immunity may be more effective than humoral (i.e., mediated by class II HLA molecules) immunity. Several genetic studies have tested for the involvement of *HLA* class II alleles, although consistent associations across study cohorts have been lacking (33, 34). *DRB1*13* has been reported to confer a protective effect (94, 95), but in other studies, two haplotypes containing this allele have been

associated with increased risk of AIDS progression (19, 96). Inadequate sample size, contributing to significant but not generalizable associations, probably accounts for the discrepant results. In a recent study of 21 acutely HIV-1–infected patients receiving combination antiretroviral drugs, the *HLA* class II haplotype *DRB1*13-DQB1*06* was present only among individuals who maintained virus suppression at every time point measured post-treatment (97). Viral suppression among individuals with this haplotype correlated with higher mean lymphoproliferation and gamma-interferon production relative to that observed among patients with other haplotypes. Such studies, in which genetic epidemiological data are correlated with functional measurements, provide solid evidence for the involvement of specific *HLA* class II alleles in resistance to HIV-1.

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LITERATURE CITED

1. Roberts JD, Bebenek K, Kunkel TA. 1988. The accuracy of reverse transcriptase from HIV-1. *Science* 242:1171–73
2. Preston BD, Poiesz BJ, Loeb LA. 1988. Fidelity of HIV-1 reverse transcriptase. *Science* 242:1168–71
3. Mansky LM, Temin HM. 1995. Lower in vivo mutation rate of human immunodeficiency virus type 1 than that predicted from the fidelity of purified reverse transcriptase. *J. Virol.* 69:5087–94
4. McMichael AJ, Rowland-Jones SL. 2001. Cellular immune responses to HIV. *Nature* 410:980–87
5. Allen TM, O'Connor DH, Jing P, et al. 2000. Tat-specific cytotoxic T lymphocytes select for SIV escape variants during resolution of primary viraemia. *Nature* 407:386–90
6. O'Connor DH, Allen TM, Vogel TU, et al. 2002. Acute phase cytotoxic T lymphocyte escape is a hallmark of simian immunodeficiency virus infection. *Nat. Med.* 8:493–99
7. Carrington M, Nelson G, O'Brien SJ. 2001. Considering genetic profiles in functional studies of immune responsiveness to HIV-1. *Immunol. Lett.* 79:131–40
8. Michael NL. 1999. Host genetic influences on HIV-1 pathogenesis. *Curr. Opin. Immunol.* 11:466–74
9. O'Brien SJ, Moore JP. 2000. The effect of genetic variation in chemokines and their receptors on HIV transmission and progression to AIDS. *Immunol. Rev.* 177:99–111
10. O'Brien SJ, Nelson GW, Winkler CA, Smith MW. 2000. Polygenic and multifactorial disease gene association in man: lessons from AIDS. *Annu. Rev. Genet.* 34:563–91
11. Dupont B, ed. 1995. *Immunobiology of HLA.* New York: Springer-Verlag

11a. Klein J, ed. 1986. *Natural History of the Major Histocompatibility Complex.* New York: Wiley

12. Hughes AL, Nei M. 1988. Pattern of nucleotide substitution at major histocompatibility complex class I loci reveals overdominant selection. *Nature* 335:167–70
13. Hughes AL, Nei M. 1989. Nucleotide substitution at major histocompatibility complex class II loci: evidence for overdominant selection. *Proc. Natl. Acad. Sci. USA* 86:958–62
14. Parham P, Ohta T. 1996. Population biology of antigen presentation by MHC class I molecules. *Science* 272:67–74

15. Hughes AL, Yeager M. 1998. Natural selection at major histocompatibility complex loci of vertebrates. *Annu. Rev. Genet.* 32:415–35
16. Doherty PC, Zinkernagel RM. 1975. A biological role for the major histocompatibility antigens. *Lancet* 1:1406–9
17. Aguado B, et al. 1999. Complete sequence and gene map of a human major histocompatibility complex. The MHC sequencing consortium. *Nature* 401:921–23
18. Obst R, Armandola EA, Nijenhuis M, et al. 1995. TAP polymorphism does not influence transport of peptide variants in mice and humans. *Eur. J. Immunol.* 25:2170–76
19. Kaslow RA, Carrington M, Apple R, et al. 1996. Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. *Nat. Med.* 2:405–11
20. Powis SJ, Deverson EV, Coadwell WJ, et al. 1992. Effect of polymorphism of an MHC-linked transporter on the peptides assembled in a class I molecule. *Nature* 357:211–15
21. Klitz W, Stephens JC, Grote M, Carrington M. 1995. Discordant patterns of linkage disequilibrium of the peptide-transporter loci within the HLA class II region. *Am. J. Hum. Genet.* 57:1436–44
22. Bugawan TL, Klitz W, Blair A, Erlich HA. 2000. High-resolution HLA class I typing in the CEPH families: analysis of linkage disequilibrium among HLA loci. *Tissue Antigens* 56:392–404
23. Tiwari JL, Terasaki PI. 1985. *HLA and Disease Associations.* New York: Springer-Verlag
24. Cooke GS, Hill AV. 2001. Genetics of susceptibility to human infectious disease. *Nat. Rev. Genet.* 2:967–77
25. Hill AV, Allsopp CE, Kwiatkowski D, et al. 1991. Common West African HLA antigens are associated with protection from severe malaria. *Nature* 352:595–600
26. Brahmajothi V, Pitchappan RM, Kakkanaiah VN, et al. 1991. Association of pulmonary tuberculosis and HLA in south India. *Tubercle* 72:123–32
27. Visentainer JE, Tsuneto LT, Serra MF, et al. 1997. Association of leprosy with HLA–DR2 in a Southern Brazilian population. *Braz. J. Med. Biol. Res.* 30:51–59
28. Thio CL, Thomas DL, Goedert JJ, et al. 2001. Racial differences in HLA class II associations with hepatitis C virus outcomes. *J. Infect. Dis.* 184:16–21
29. Thursz M, Yallop R, Goldin R, et al. 1999. Influence of MHC class II genotype on outcome of infection with hepatitis C virus. The HENCORE group. Hepatitis C European Network for Cooperative Research. *Lancet* 354:2119–24
30. Cramp ME, Carucci P, Underhill J, et al. 1998. Association between HLA class II genotype and spontaneous clearance of hepatitis C viraemia. *J. Hepatol.* 29:207–13
31. Thursz MR, Kwiatkowski D, Allsopp CE, et al. 1995. Association between an MHC class II allele and clearance of hepatitis B virus in the Gambia. *N. Engl. J. Med.* 332:1065–69
32. Hohler T, Gerken G, Notghi A, et al. 1997. HLA-DRB1*1301 and *1302 protect against chronic hepatitis B. *J. Hepatol.* 26:503–7
33. Just JJ. 1995. Genetic predisposition to HIV-1 infection and acquired immune deficiency virus syndrome: a review of the literature examining associations with HLA. *Hum. Immunol.* 44:156–69. Erratum. 1998. *Hum. Immunol.* 45:78
34. Keet IP, Klein MR, Just JJ, Kaslow RA. 1996. The role of host genetics in the natural history of HIV-1 infection: the needles in the haystack. *AIDS* 10:S59–67
35. O'Brien SJ, Gao X, Carrington M. 2001. HLA and AIDS: a cautionary tale. *Trends Mol. Med.* 7:379–81
36. Doherty PC, Zinkernagel RM. 1975. Enhanced immunological surveillance in mice heterozygous at the H-2 gene complex. *Nature* 256:50–52

37. Zinkernagel RM. 1996. Immunology taught by viruses. *Science* 271:173–78
38. Carrington M, Nelson GW, Martin MP, et al. 1999. HLA and HIV-1: heterozygote advantage and B*35-Cw*04 disadvantage. *Science* 283:1748–52
39. Tang J, Costello C, Keet IP, et al. 1999. HLA class I homozygosity accelerates disease progression in human immunodeficiency virus type 1 infection. *AIDS Res. Hum. Retroviruses* 15:317–24
40. Goulder P, Price D, Nowak M, et al. 1997. Co-evolution of human immunodeficiency virus and cytotoxic T-lymphocyte responses. *Immunol. Rev.* 159:17–29
41. McMichael A, Klenerman P. 2002. HIV/AIDS HLA leaves its footprints on HIV. *Science* 296(5572):1410–11
42. Haynes BF, Pantaleo G, Fauci AS. 1996. Toward an understanding of the correlates of protective immunity to HIV infection. *Science* 271:324–28
43. Rowland-Jones S, Tan R, McMichael A. 1997. Role of cellular immunity in protection against HIV infection. *Adv. Immunol.* 65:277–346
44. Detels R, Liu Z, Hennessey K, et al. 1994. Resistance to HIV-1 infection. Multicenter AIDS Cohort Study. *J. Acquir. Immune Defic. Syndr.* 7:1263–69
45. Salkowitz JR, Purvis SF, Meyerson H, et al. 2001. Characterization of high-risk HIV-1 seronegative hemophiliacs. *Clin. Immunol.* 98:200–11
46. Vlahov D, Polk BF. 1988. Perspectives on infection with HIV-1 among intravenous drug users. *Psychopharmacol. Bull.* 24:325–29
47. Migueles SA, Sabbaghian MS, Shupert WL, et al. 2000. HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. *Proc. Natl. Acad. Sci. USA* 97:2709–14
48. Gao X, Nelson GW, Karacki P, et al. 2001. Effect of a single amino acid change in MHC class I molecules on the rate of progression to AIDS. *N. Engl. J. Med.* 344:1668–75
49. Hendel H, Caillat-Zucman S, Lebuanec H, et al. 1999. New class I and II HLA alleles strongly associated with opposite patterns of progression to AIDS. *J. Immunol.* 162:6942–46
50. Magierowska M, Theodorou I, Debre P, et al. 1999. Combined genotypes of CCR5, CCR2 SDF1, and HLA genes that can predict the long-term nonprogressor status in human immunodeficiency virus–1–infected individuals. *Blood* 93:936–41
51. Scorza Smeraldi R, Fabio G, Lazzarin A, et al. 1986. HLA-associated susceptibility to acquired immunodeficiency syndrome in Italian patients with human-immunodeficiency-virus infection. *Lancet* 2:1187–89
52. Itescu S, Mathur-Wagh U, Skovron ML, et al. 1992. HLA-B35 is associated with accelerated progression to AIDS. *J. Acquir. Immune Defic. Syndr.* 5:37–45
53. Sahmoud T, Laurian Y, Gazengel C, et al. 1993. Progression to AIDS in French haemophiliacs: association with HLA-B35. *AIDS* 7:497–500
54. Klein MR, Keet IP, D'Amaro J, et al. 1994. Associations between HLA frequencies and pathogenic features of human immunodeficiency virus type 1 infection in seroconverters from the Amsterdam cohort of homosexual men. *J. Infect. Dis.* 169:1244–49
55. Muller CA, Engler-Blum G, Gekeler V, et al. 1989. Genetic and serological heterogeneity of the supertypic HLA-B locus specificities Bw4 and Bw6. *Immunogenetics* 30:200–7
56. Flores-Villanueva PO, Yunis EJ, Delgado JC, et al. 2001. Control of HIV-1 viremia and protection from AIDS are associated with HLA-Bw4 homozygosity. *Proc. Natl. Acad. Sci. USA* 98:5140–45
57. Gumperz JE, Litwin V, Phillips JH, et al. 1995. The Bw4 public epitope of HLA-B molecules confers reactivity with natural killer cell clones that express NKB1,

a putative HLA receptor. *J. Exp. Med.* 181:1133–44
58. Costello C, Tang J, Rivers C, et al. 1999. HLA-B*5703 independently associated with slower HIV-1 disease progression in Rwandan women. *AIDS* 13:1990–91
59. Klein MR, van der Burg SH, Hovenkamp E, et al. 1998. Characterization of HLA-B57-restricted human immunodeficiency virus type 1 Gag- and RT-specific cytotoxic T lymphocyte responses. *J. Gen. Virol.* 79:2191–201
60. Goulder PJ, Bunce M, Krausa P, et al. 1996. Novel, cross-restricted, conserved, and immunodominant cytotoxic T lymphocyte epitopes in slow progressors in HIV type 1 infection. *AIDS Res. Hum. Retroviruses* 12:1691–98
61. Gillespie GM, Kaul R, Dong T, et al. 2002. Cross-reactive cytotoxic T lymphocytes against a HIV-1 p24 epitope in slow progressors with B*57. *AIDS* 16:961–72
62. Goulder PJ, Tang Y, Pelton SI, Walker BD. 2000. HLA-B57-restricted cytotoxic T-lymphocyte activity in a single infected subject toward two optimal epitopes, one of which is entirely contained within the other. *J. Virol.* 74:5291–99
63. Betts MR, Krowka J, Santamaria C, et al. 1997. Cross-clade human immunodeficiency virus (HIV)–specific cytotoxic T-lymphocyte responses in HIV-infected Zambians. *J. Virol.* 71:8908–11
64. Cao H, Kanki P, Sankale JL, et al. 1997. Cytotoxic T-lymphocyte cross-reactivity among different human immunodeficiency virus type 1 clades: implications for vaccine development. *J. Virol.* 71:8615–23
65. Durali D, Morvan J, Letourneur F, et al. 1998. Cross-reactions between the cytotoxic T-lymphocyte responses of human immunodeficiency virus–infected African and European patients. *J. Virol.* 72: 3547–53
66. Goulder PJ, Phillips RE, Colbert RA, et al. 1997. Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS. *Nat. Med.* 3:212–17
67. Nixon DF, Townsend AR, Elvin JG, et al. 1988. HIV-1 gag-specific cytotoxic T lymphocytes defined with recombinant vaccinia virus and synthetic peptides. *Nature* 336:484–87
68. Rammensee HG, Friede T, Stevanoviic S. 1995. MHC ligands and peptide motifs: first listing. *Immunogenetics* 41:178–228
69. Jardetzky TS, Lane WS, Robinson RA, et al. 1991. Identification of self peptides bound to purified HLA-B27. *Nature* 353:326–29
70. Nietfield W, Bauer M, Fevrier M, et al. 1995. Sequence constraints and recognition by CTL of an HLA-B27-restricted HIV-1 gag epitope. *J. Immunol.* 154: 2189–97
71. Kelleher AD, Long C, Holmes EC, et al. 2001. Clustered mutations in HIV-1 gag are consistently required for escape from HLA-B27-restricted cytotoxic T lymphocyte responses. *J. Exp. Med.* 193:375–86
72. Goulder PJ, Brander C, Tang Y, et al. 2001. Evolution and transmission of stable CTL escape mutations in HIV infection. *Nature* 412:334–38
73. Kaslow RA, Rivers C, Tang J, et al. 2001. Polymorphisms in HLA class I genes associated with both favorable prognosis of human immunodeficiency virus (HIV) type 1 infection and positive cytotoxic T-lymphocyte responses to ALVAC-HIV recombinant canarypox vaccines. *J. Virol.* 75:8681–89
74. Hill AV, Elvin J, Willis AC, et al. 1992. Molecular analysis of the association of HLA-B53 and resistance to severe malaria. *Nature* 360:434–39
75. Falk K, Rotzschke O, Grahovac B, et al. 1993. Peptide motifs of HLA-B-35 and B37 molecules. *Immunogenetics* 38:161–62
76. Saper MA, Bjorkman PJ, Wiley DC. 1991. Refined structure of the human histocompatibility antigen HLA-A2 at 2.6 A resolution. *J. Mol. Biol.* 219:277–319

77. Silver ML, Guo HC, Strominger JL, Wiley DC. 1992. Atomic structure of a human MHC molecule presenting an influenza virus peptide. *Nature* 360:367–69
78. Guo HC, Jardetzky TS, Garrett TP, et al. 1992. Different length peptides bind to HLA-Aw68 similarly at their ends but bulge out in the middle. *Nature* 360:364–66
79. Hildebrand WH, Turnquist HR, Prilliman KR, et al. 2002. HLA class I polymorphism has a dual impact on ligand binding and chaperone interaction. *Hum. Immunol.* 63:248–55
80. Williams AP, Peh CA, Purcell AW, et al. 2002. Optimization of the MHC class I peptide cargo is dependent on tapasin. *Immunity* 16:509–20
81. Neisig A, Wubbolts R, Zang X, et al. 1996. Allele-specific differences in the interaction of MHC class I molecules with transporters associated with antigen processing. *J. Immunol.* 156:3196–206
82. Ferrara GB, Bacigalupo A, Lamparelli T, et al. 2001. Bone marrow transplantation from unrelated donors: the impact of mismatches with substitutions at position 116 of the human leukocyte antigen class I heavy chain. *Blood* 98:3150–55
83. MacDonald KS, Embree J, Njenga S, et al. 1998. Mother-child class I HLA concordance increases perinatal human immunodeficiency virus type 1 transmission. *J. Infect. Dis.* 177:551–56
84. Lockett SF, Robertson JR, Brettle RP, et al. 2001. Mismatched human leukocyte antigen alleles protect against heterosexual HIV transmission. *J. Acquir. Immune Defic. Syndr.* 27:277–80
85. MacDonald KS, Embree JE, Nagelkerke NJ, et al. 2001. The HLA A2/6802 supertype is associated with reduced risk of perinatal human immunodeficiency virus type 1 transmission. *J. Infect. Dis.* 183:503–6
86. MacDonald KS, Fowke KR, Kimani J, et al. 2000. Influence of HLA supertypes on susceptibility and resistance to human immunodeficiency virus type 1 infection. *J. Infect. Dis.* 181:1581–89
87. Sidney J, Grey HM, Kubo RT, Sette A. 1996. Practical, biochemical and evolutionary implications of the discovery of HLA class I supermotifs. *Immunol. Today* 17:261–66
88. del Guercio MF, Sidney J, Hermanson G, et al. 1995. Binding of a peptide antigen to multiple HLA alleles allows definition of an A2-like supertype. *J. Immunol.* 154:685–93
89. McKenzie LM, Pecon-Slattery J, Carrington M, O'Brien SJ. 1999. Taxonomic hierarchy of HLA class I allele sequences. *Genes Immun.* 1:120–29
90. Rowland-Jones S, Sutton J, Ariyoshi K, et al. 1995. HIV-specific cytotoxic T-cells in HIV-exposed but uninfected Gambian women. *Nat. Med.* 1:59–64
91. Rowland-Jones SL, Dong T, Fowke KR, et al. 1998. Cytotoxic T cell responses to multiple conserved HIV epitopes in HIV-resistant prostitutes in Nairobi. *J. Clin. Invest.* 102:1758–65
92. Kaul R, Plummer FA, Kimani J, et al. 2000. HIV-1-specific mucosal CD8+ lymphocyte responses in the cervix of HIV-1-resistant prostitutes in Nairobi. *J. Immunol.* 164:1602–11
93. Kaul R, Rowland-Jones SL, Kimani J, et al. 2001. Late seroconversion in HIV-resistant Nairobi prostitutes despite pre-existing HIV-specific CD8+ responses. *J. Clin. Invest.* 107:341–49
94. Chen Y, Winchester R, Korber B, et al. 1997. Influence of HLA alleles on the rate of progression of vertically transmitted HIV infection in children: association of several HLA-DR13 alleles with long-term survivorship and the potential association of HLA-A*2301 with rapid progression to AIDS. Long-Term Survivor Study. *Hum. Immunol.* 55:154–62
95. Itescu S, Rose S, Dwyer E, Winchester R. 1994. Certain HLA-DR5 and -DR6 major histocompatibility complex class II alleles are associated with a CD8

lymphocytic host response to human immunodeficiency virus type 1 characterized by low lymphocyte viral strain heterogeneity and slow disease progression. *Proc. Natl. Acad. Sci. USA* 91:11472–76

96. Kroner BL, Goedert JJ, Blattner WA, et al. 1995. Concordance of human leukocyte antigen haplotype-sharing, CD4 decline and AIDS in hemophilic siblings. Multicenter Hemophilia Cohort and Hemophilia Growth and Development Studies. *AIDS* 9:275–80
97. Malhotra U, Holte S, Dutta S, et al. 2001. Role for HLA class II molecules in HIV-1 suppression and cellular immunity following antiretroviral treatment. *J. Clin. Invest.* 107:505–17

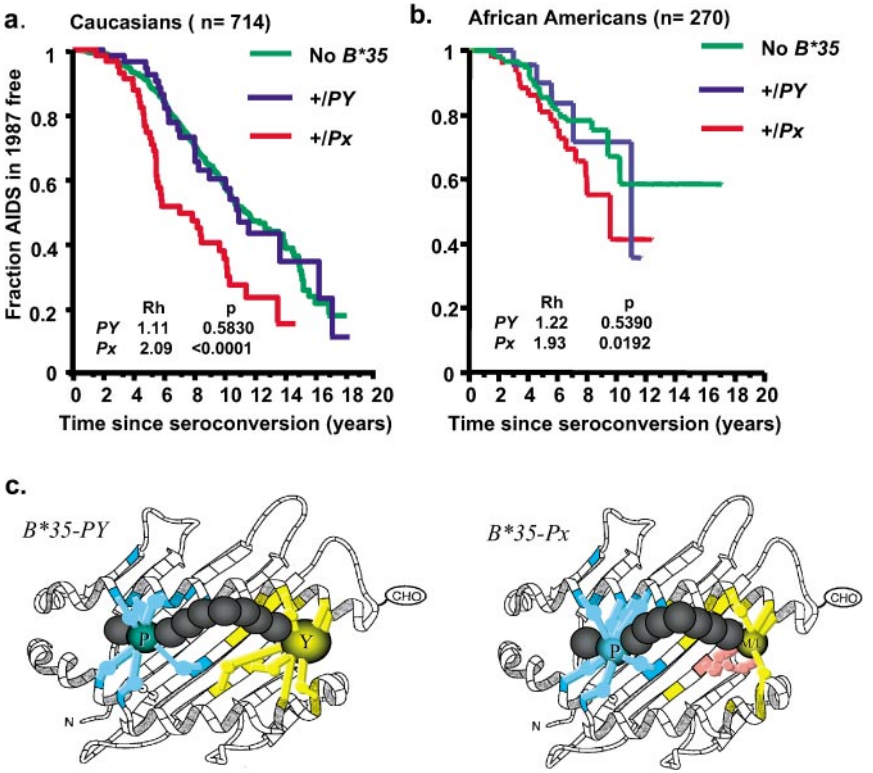

Figure 3 Susceptibility effect of HLA-B*35-Px on progression to AIDS among (a) Caucasian and (b) African American patients in 1987. Relative hazards (RH) and p values are given for patients with one copy of HLA-B*35-PY (B*3501 or B*3508) (blue curve), one copy of B*35-Px (B*3502, B*3503, B*3504, or B*5301) (red curve), and patients with no B*35-Px or B*35-PY (green curve). Only patients who are heterozygous for HLA-B were considered in the analysis, to exclude any effect of homozygosity at this locus. (c) The B*35-PY molecules prefer to bind peptides with tyrosine (Y) at the carboxy terminus, whereas the B*35-Px molecules have no single preference at P9 (M/L) and do not bind peptides that have tyrosine at the carboxy terminus. This difference may result in an inappropriate response in patients with B*35-Px compared to a relatively protective response in patients with B*35-PY.

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