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Patterns of ethnic diversity among the genes that influence AIDS

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Although HIV-1/AIDS emerged late in the last century, more than 42 million individuals have been infected and 25 million have died worldwide, making AIDS, like malaria, a strong selective force for disease-associated genetic factors. Many of the genes that mediate immune response or that are co-opted by HIV-1 for completion of its lifecycle show differences in allele frequencies, as a result of drift, migration or selection. Here we show that the majority of AIDS candidate genes and AIDS restriction genes show significant differences in allele frequencies, possibly the result of historic selective pressures. These genes are undergoing present day natural selection in populations with high AIDS prevalence.

INTRODUCTION

Since the geographic dispersal of modern humans 100 000–150 000 years ago, the human genome has been shaped by evolutionary and historical forces (1–4). The migration out of Africa to Asia and Europe, estimated to have involved an effective population size of 10 000 (5,6), was followed by rapid expansion of human populations, tending to limit both allele and haplotype diversity in non-African populations relative to African populations (7). Recent migratory events, such as the forced removal of people from western Africa to colonies in the Americas and diaspora of many ethnic groups have also shaped human populations by genetic admixture (8–11). In addition, periodic outbreaks of deadly infectious agents and regional environmental pressures have modified the genetic architecture of disease gene allelic variation in local human populations (12,13).

The best evidence for the influence of human pathogens on natural selection comes from studies of host genetic resistance to malaria and AIDS. Malaria became endemic 6000–10 000 years ago, coincident with the rise of agriculture, while AIDS emerged within the last 30 years (14–18). Malaria causes significant mortality, particularly among children and pregnant women, and this selective pressure over 300–500 generations has resulted in adaptive shifts in the allele frequency of several genes with a role in malaria resistance (12,18–21). Among these are: the X-linked glucose-6-phosphate dehydrogenase (*G6pd*), the Duffy antigen receptor for chemokines (*DARC*), and the α- and β-globin genes, each of which show geographical differences in allele frequencies correlated with the occurrence of malaria (12,18,21–23). Association studies have also implicated *HLA*-B and *HLA*-DR, *ICAM*-1, *TNF*, *NOS* type 2 and *CD*36 as having a modifying role in malaria susceptibility and resistance (reviewed in 12). Recent studies have shown that the strong selective pressure of malaria in sub-Saharan Africa has left its signature in the form of extended haplotype homozygosity (EHH) of core haplotypes containing the *G6PD* resistance allele (24–27) corresponding to a population expansion within the last 6000–10 000 years.

There is also mounting evidence that the *CCR5* gene, which specifies an HIV-1 co-receptor, has undergone recent selection, probably by a pathogen such as *Variola* (small pox) or *Yersinia pestis* (bubonic plague) (28–31). Both the *cis*-regulatory region of the *CCR5* and the exonic *CCR5*-Δ32 show subtle signatures of historic selection. First, the promoter region variation was found to have higher than expected common polymorphisms suggestive of balancing selection (29). Second, *CCR5*-Δ32 allele frequency is distributed as a north to south gene frequency gradient across Europe, with a high of 15% in Scandinavia, 10% in Britain, France and Germany, 5% in Italy, Greece and Turkey, and 0% in Arabian Peninsula (28). The *CCR5*-Δ32 mutation arose in northern Europe within historic times, but experienced a recent and rapid expansion in allele frequency to ∼10–14% in northern Europeans (28). Coalescent calculations based upon the size of extended linkage disequilibrium around *CCR5*-Δ32 suggest that the most recent strong selective pressure occurred around 700 years ago (28).

Approximately 85–95% of human genetic variation is shared among the major ethnic groups, sub-Saharan Africans, Europeans and East Asians, whereas only 5–15% of the global

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variation is distinctive for ethnic groups (32–35). Genes that encode proteins required for reproductive, developmental and housekeeping functions that have evolved for maximum fitness tend to display shared allele variation among distinct ethnicities, whereas genes that encode factors involved in immunity, are required by pathogens for completion of their lifecycle or are required for homeostasis may be under varying selective pressure for change. It is likely that a fair proportion of ethnic genetic divergence reflects historic and recent selective pressures from local influences (microbial or ecological) that occurred on different continents (35).

In the two decades since the discovery of AIDS, more than 60 million people have been infected with HIV-1 and 25 million have died (www.unaids.org). The geographic distribution of HIV-1/AIDS is skewed with more than 75% of HIV-1 infections and 84% of all AIDS-related deaths occurring in Africa. Of 44 countries in sub-Saharan Africa, only four have an adult prevalence rate of less than 1% while 16 have a prevalence rate >10% and of these seven report prevalence rates greater than 20%. The southern African HIV-1/AIDS epidemic has been explosive, with 25% of South African adults and 39% of Botswanian adults HIV-1-infected. Mortality in eastern and southern Africa is predicted to be 50–500% higher with AIDS than without AIDS (www.who.int/emc-hiv). Although HIV-1/AIDS is too recent to have had a strong selective impact on host genes, Slatkin and colleagues have modeled the effects of HIV-1-mediated selection for resistant *CCR2* and *CCR5* genotypes, predicting a modest 2–4 year increase or decrease in survival for South Africa, a country of high HIV-1 prevalence (30,31). The model projected that within 100 years resistance genotype frequencies will increase from 40 to 53% while the susceptible genotypes will decrease from 20 to 10%, leading to a mean increase in AIDS-free survival from 7.8 to 8.8 years.

AIDS RESTRICTION GENES (ARGs)

HIV-1 infection causes a progressive loss of CD4 T cells, resulting in a disabled immune system unable to combat a range of adventitious pathogens. However, there is considerable heterogeneity among individuals in infection susceptibility, in the time required to deplete the CD4 T-lymphocyte population and to develop AIDS-defining diseases (17,36–38). Although a myriad of social and economic factors strongly influence the HIV-1 pandemic, virologic and host genetic factors probably account for a portion of the observed epidemiological heterogeneity in infection susceptibility and in progression rates (39–46). Host genetic variation, particularly in genetic factors directly involved in HIV-1 cell entry, immune recognition and antigen presentation, have been shown to profoundly modify individual response to HIV-1 exposure, infection and pathogenesis (45–58).

Host factors critical to the successful completion of the HIV-1 life cycle and for the immune response to HIV-1 infection have been extensively described: this vast literature has provided investigators with an abundance of plausible candidate genes for genetic analysis. A series of investigations in 1995/1996 demonstrated that the chemokines RANTES, MIP-1α and MIP-1β blocked R5 (macrophage-tropic) HIV-1 infection while SDF blocked X4 (T cell line-tropic) HIV-1 infection, implicating the corresponding chemokine coreceptors CCR5 and CXCR4 as entry portals for HIV-1 infection (59–62). These findings demonstrated the role of cell-entry factors in HIV-1 transmission and pathogenesis. The discovery that the *CCR5*-Δ32, a 32 base pair deletion in the chemokine receptor gene, provided near complete protection from HIV-1 infection in homozygotes and a 2–4 year delay in progression to AIDS in heterozygotes (54,63–65) confirmed the critical importance of the *CCR5* co-receptor in HIV-1 transmission. Once HIV-1 has gained entrance to the CD4+ cell via fusion and endocytosis, continued interactions with host factors are required for successful completion of the viral lifecycle (reviewed in 66).

In an effort to discover genes that provide resistance to HIV-1/AIDS, candidate genes connected to HIV-1 disease and host immune response were selected to search for DNA variants in 72 African American (AA), 72 European American (EA), and 32 Han Chinese. Figure 1 presents a summary of polymorphic variants in 36 candidate ARGs identified by single-strand conformational polymorphism, RNA cleavage assays, and by resequencing the upstream promoter, 5′ and 3′ untranslated regions, introns and exons. In the chemokine receptor group, non-synonymous changes resulting in amino acid replacement are common, probably accumulated as a consequence of pathogen-mediated selection. For example, a historical succession of diseases probably imposed a positive selection favoring carriers of null mutations in the chemokine receptors *CCR5* and the Duffy Antigen Receptor for Chemokines (*DARC*) (21,30,31). The *CCR5*-Δ32 mutation introduces a premature stop codon leading to a knockout phenotype in homozygotes blocking HIV-1 cell entry. Similarly, the *Fy* null mutation in the *DARC* promoter region eliminates the DNA-binding site for the erythroid transcriptional factor GATA 1, leading to altered expression in erythrocytes (but not in other cell types), effectively preventing infection by *Plasmodium vivax* (67). Chemokine receptors also have been co-opted by other human and non-human pathogens for cell entry (68): for example, the *CCR5* ortholog in rabbits is the cell-entry receptor for myxoma, a virus closely related to smallpox (69). The ability of chemokine receptors to tolerate amino acid substitutions may provide a successful strategy to evade pathogen cell entry via chemokine receptors (70,71).

The genes encoding cytokines and chemokines involved in cell trafficking and modulation of the immune response show few non-synonymous changes but considerable variation in regulatory promoter regions (Fig. 1). It may be that any amino acid variation in exons leads to deleterious structural change affecting binding kinetics to their receptors. Abundant variation in these genes' regulatory regions, on the other hand, may reflect the fact that these factors are under countervailing selective pressures: higher levels of inflammation may be protective against pathogens, but lead to autoimmunity or atopy (72). Variants in the regulation of chemokines and cytokines can alter pathways of the inflammatory and immune response. For example, the switch between TH1 (predominantly cellular) and TH2 (predominantly humoral) immune responses is believed to play a role in AIDS pathogenesis and could explain the AIDS accelerating effect of the down-regulating 5′A *IL*10 variant (73–76). Further, high levels of chemokines may act

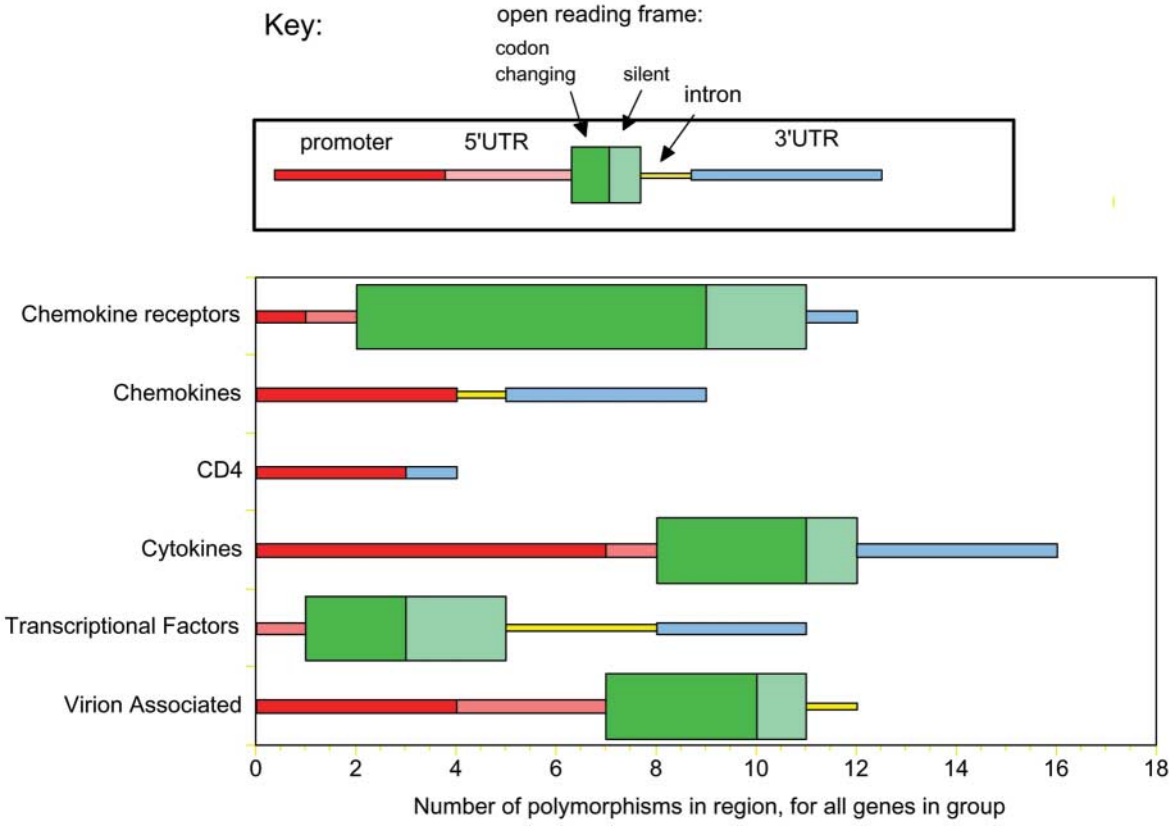

Figure 1. Schematic graph of number of mutations found in different gene regions for six categories of AIDS candidate genes. Note the preponderance of codon changing mutations among chemokine receptors, and in contrast the absence of exonic mutations among chemokines.

against pathogens simply by reducing the number of their cognate receptors, which certain viruses may employ for cell entry.

There is only one documented fixed allele difference between major ethnic groups, the *DARC Fy* T/C polymorphism where the *Fy* C null allele restricts *P. vivax* cell-entry is in sub-Saharan Africans exclusively (77). Among other potential disease genes among populations descending from the three major continents, Asia, Europe and Africa, there occur considerable differences in allele frequencies (2,46,78–80). Figure 2 shows a comparison of allele frequencies of 64 SNP alleles discovered in 36 candidate ARGs (Fig. 1) among European American (EA), African American (AA) and Han Chinese samples, representing at least 1000 each AA and EA and 100 Han Chinese. One-third of the genes shows similar allele frequencies in all three ethnic groups while the others show from 10 to 60% differences in allele frequencies between ethic groups. These frequency differences surely affect the overall genetic milieu for diseases genes, thereby possibly modifying the effects of a causal disease gene in different geographic or ethnic populations. In addition, allele frequency differences will also change haplotype frequencies and structure, in some cases modifying the effects of causal genes through *cis* gene–gene interactions.

Table 1 presents a list of ARGs identified as susceptibility or resistance factors in five USA-based AIDS cohorts (46). Of 15 genetic factors listed, nine have ≥5% and five have ≥15% difference in frequency between AA and EA. Differences in allele frequencies of genes that mediate disease resistance can be an advantage in association mapping since ethnic mixing generates temporary long-range linkage disequilibrium (LD) as a consequence of admixture (9–11). In African Americans the proportion of European genes may range from 7 to 30% (34,81,82). Detectible LD may extend for several centimorgans and persist for 15–20 generations, facilitating the identification of causal genes (10,11). On the other hand, population structure occurring as a result of mutation, drift and selection may complicate the identification of restriction genes and confound analysis of genetic factors. It therefore should not be unexpected that even true causal alleles may show different effects in different populations.

Table 2 presents discovered haplotypes surrounding three documented ARGs: *RANTES*, *CCR2-CCR5* and *MCP1-Eotaxin* (56,79,83). The *CCR2-CCR5* gene cluster specifies three alleles (*CCR5*-Δ32, *CCR5-P1* and *CCR2-64I*) associated with HIV-1 progression and infection susceptibility (Table 3). Both *CCR2-64I* and *CCR5*-Δ32 are protective while the ⟨+.*P1*.+⟩ haplotype is accelerating. *CCR2*-64I and *CCR5*-Δ32 occur on a *CCR5-P1*-bearing haplotype, but never together. Both *CCR5*-Δ32 and *CCR2-64I* mitigate the accelerating effects of the *CCR5-P1* promoter haplotype. The influence of *CCR2-64I* is equivalent to that of CCR5-Δ32 in delaying AIDS by 2–4 years. The mechanism is indirect, perhaps involving differential avidity of *CCR2* allelic products in forming CCR2-CXCR4

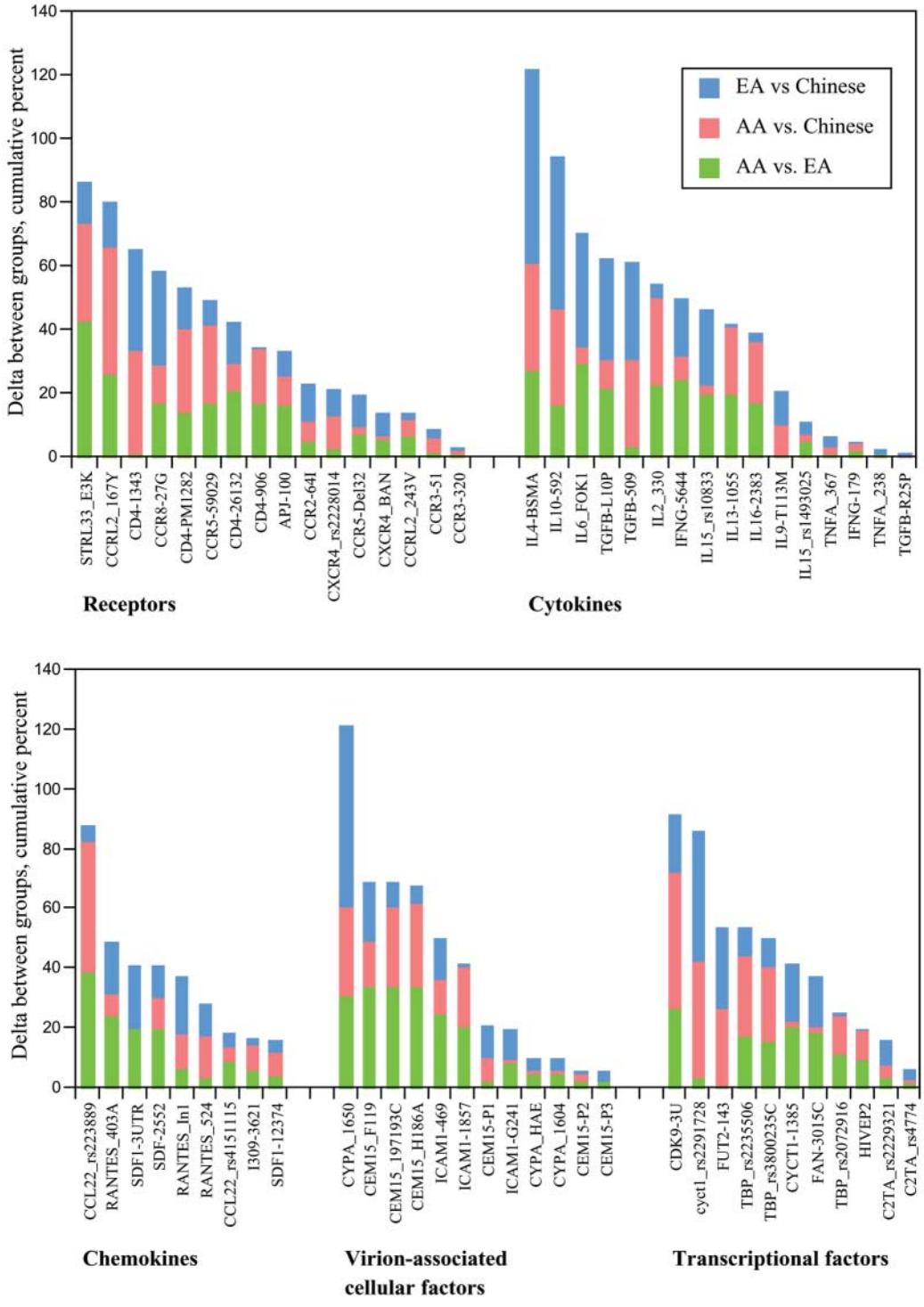

Figure 2. Variation between groups of frequency of variants—primarily SNPs—in five categories of AIDS candidate genes. Subjects are European ($n \geq 1000$) and ($n \geq 1000$) African Americans in USA-based AIDS cohorts, and volunteer normal blood donor Han Chinese ($n \geq 100$). Stacked color segments of bars show the unsigned delta, that is the smaller frequency subtracted from the larger, for each comparison.

heterodimers on the endoplasmic reticulum, thereby limiting CXCR4 availability required for the R5 to X4 tropic transition (84). The *CCR5*-Δ32 haplotype has a limited geographical distribution, while the *CCR2*-64I and ⟨+.*P1*.+⟩ haplotypes are common across ethnic populations (28,46–52,85).

Elevated RANTES levels have been observed in high-risk HIV-1 uninfected individuals and also in HIV-1 infected persons who maintain high CD4 T cell counts (86–89). Several groups have reported that *RANTES* regulatory variants are associated modified HIV-1 infection or progression rates by the variants in regulatory

Table 1. Allele frequencies for AIDS restriction genes in three racial groups

	Allele or factor	Genetic model	African American	European American	Delta AA versus EA	Han Chinese	References
Resistant factors							
CCR5	Δ32	Recessive	0.02	0.10	0.08	Not observed	(54)
CCR2	64I	Dominant	0.15	0.10	0.05	0.25	(58)
SDF1	3′A	Recessive	0.02	0.21	0.19	0.26	(47)
CXCR6	E3K	Dominant	0.44	0.006	0.43	0.133	(98)
MCP1.MCP 3.Eotaxin	Hap 7	Dominant	0.031	0.192	0.16	ND	(83)
HLA	B*27	Co-dominant	0.01	0.041	0.03	ND	(49)
HLA	B*57	Co-dominant	0.06	0.04	0.02	ND	(49)
KIR-HLA	SDS1-Bw4-80I	Epistatic	0.08	0.12	0.04		(57)
Susceptible factors							
IL10	5′A	Dominant	0.4	0.24	0.16	0.6	(76)
IFNG	179T	Dominant	0.02	0.001	0.02	Not observed	(97)
RANTES	In1.1C	Dominant	0.20	0.14	0.06	0.30	(79)
HLA	B*35	Dominant	0.07	0.09	0.02	ND	(100)
HLA	B*35*Px	Dominant	0.09	0.03	0.06	ND	(100)
CCR5	+.P1.+	Dom/rec	0.25	0.56	0.31	0.44	(56,51)
HLA class I	1 locus homozygosity	Co-dominant	0.16	0.22	0.08	ND	(99)
HLA class II	Two or three loci homozygosity	Co-dominant	0.03	0.06	0.03	ND	(99)

Table 2. Population frequencies of haplotypes associated with HIV-1 infection[a] or progression to AIDS[b]

Genes/loci				Haplotype	Haplotype frequency	
					AA	EA
CCR2-CCR5[a]						
CCR2 64	CCR5 Promoter		CCR5 ORF			
V	P1		+	+.P1.+	0.26	0.36
V	P2–4		+	+.P2-4.+	0.57	0.58
V	P1		Δ32	+.P1.Δ32	0.02	0.10
I	P1		+	I.P1.+	0.16	0.10
RANTES						
−403	−28	In1.1	3′222			
G	C	T	T	R1	0.57	0.77
A	C	T	T	R2	0.16	0.05
A	C	C	T	R3	0.13	0.003
A	C	C	C	R4	0.07	0.11
A	G	C	T	R5	0.002	0.025
MCP1.Eotaxin[c]						
MCP1-2136	MCP1 767		Eotaxin 1385			
A	C		G	H1–6,8	0.90	0.77
T	G		A	H7	0.03	0.19

[a]Diplotypes providing resistance to HIV-1 infection: +.P1.Δ32/+.P1. Δ32 and H7/others.
[b]Diplotypes and haplotypes modifying progression to AIDS: protective factors—+.P1.Δ32 and 64I.P1.+, and R1/R1; accelerating factors—R3 and R4 (AA) and R3 (EA), +.P1.+ (see 54,56,58,79,83).

regions (50,79,90,91): *−28G* in the promoter region is associated with slightly higher *RANTES* levels (79,90); *−403A* has been reported to up-regulate transcription in some (91), but not other (79), studies; and *In1.1C* in the first intron potently down-regulates *RANTES* transcription (79). The frequency distribution of the *RANTES* alleles is quite different between ethnic groups (Fig. 3); although all populations retain the R2 haplotype containing −403A, the frequencies of R2 are quite different (Fig. 3). The other variant alleles also occur on haplotypes containing the −403A allele. Since the −403A allele is found in the chimpanzee as well as across human ethnic lineages, the ancestral state is −403A and the −403G allele is derivative (46,50). *RANTES-In1.1C* is in complete positive LD with −403A, while −28G and 3′C are in complete positive LD with both −403A and *In1.1C*, but in absolute negative LD with each other (Fig. 3). The −28G allele, which is common in Asians, rare in EA, and absent in Africans, appears to mitigate the accelerating effects of *In1.1C* in EA, an effect consistent with expression studies, showing that −28G weakly counters the down-regulating effect of *In1.1C* (79) (Fig. 3). The down-regulating *RANTES-In1.1C* allele is distributed across three haplotypes including R3, common in AA and infrequent in EA. In addition, as seen in Figure 3, the up-regulating −28G allele on the R5 haplotype is more common in EA as is the 3′222A-bearing R4 haplotype. The successive historical appearance of these offsetting factors in the population, as indicated by the haplotype structure, may reflect an ongoing dialectic between the benefits and disadvantages of high levels of chemokine expression.

The chemokines MCP1, MCP 3 and Eotaxin bind CCR2 and CCR3 and control the migration of immune cells to sites of inflammation and infection (92). Each has been variously implicated in HIV-1 replication or pathogenesis, possibly by attracting CD4+ cells to sites of HIV-1 infection and contributing to the propagation of HIV-1 (93–95). The *MCP1*, *MCP3* and *Eotaxin* gene cluster forms a 33 kb haplotype block Hap-7, containing three alleles in near-absolute LD, which associates with resistance to HIV-1 infection in EA (83). Haplotype 7 is frequent in EA ($f = 19\%$) but rare in AA ($f = 3\%$). The historical events contributing to the elevated frequency of Hap 7 are unknown, but may reflect historic positive selection of some combination of these immune regulation genes.

Three ARGs discovered in AA cohorts are infrequent in EA. The interferon-gamma (IFN-γ) cytokine is pivotal for the

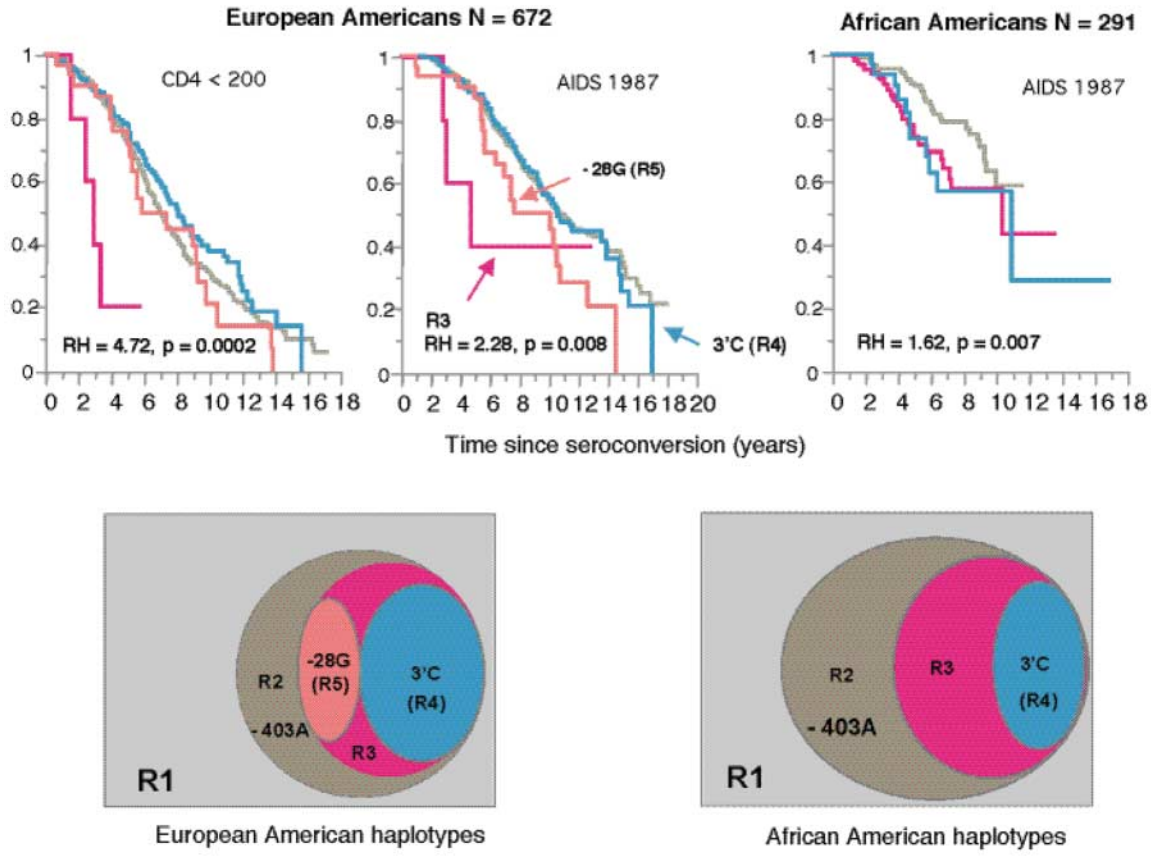

Figure 3. Effect of haplotypes carrying RANTES In1.1C on progression to AIDS in European and African Americans. At the bottom are Venn diagrams giving the relation of occurrence of the four RANTES variants −403A, In1.1C, 3′C and −28G on haplotypes; note that the red oval represents all In1.1C, so the red oval minus the haplotypes carrying 3′C and −28G (blue and orange) represents haplotype R3. At the top are Kaplan Meier survival plots keyed to the Venn diagrams. The gray lines represent subjects lacking In1.1C, i.e. carrying only R1 and/or R2; the red, blue and orange lines represent R3, R4 and R5, respectively.

development and propagation of a cytotoxic T cell response against viral pathogens. The −179T allele in the promoter region of *IFNG* is inducible by tumor necrosis factor (TNF-α) for increased IFN-γ transcription (96). Carriers for −179T allele experienced a rapid loss of CD4 T cells possibly as a result of the synergistic interaction between TNF-α and IFN-γ to induce CD4 T cell apoptosis (97). Approximately 4% of the African American population are carriers for an allele that induces aberrant regulation of a highly conserved cytokine fundamental in the immune regulation of intracellular pathogens by cytotoxic T cells.

The gene for *CXCR6*, a chemokine receptor used by SIV for cell entry, has a single non-synonymous mutation in the third exon introducing a non-conservative E3K amino acid substitution in the SIV env binding domain (98). *CXCR6*-3K has no influence on overall progression to AIDS or HIV-1 viral load, yet *CXCR6*-3K homozygotes had a significantly longer survival time after developing *Pneumocystis carinii* infection (PCP). The *CXCR6*-3K allele is found at 45% allele frequency in AA but is rare in EA (∼0.6%). The disparity in allele frequency between ethnic groups may reflect genetic drift but it is an intriguing speculation that the large frequency difference coupled with association with HIV-1 may be a hint of historic selective influence by infectious agents. High parasite burdens in Africa have been associated with immune suppression that may lead to increased susceptibility to opportunistic infections such as PCP or tuberculosis, both of which affect lungs, a site of CXCR6 expression. Even a slight survival advantage over a long period would gradually elevate allele frequencies.

The *HLA* B*35Px allele group accelerates progression to AIDS in both EA and AA, possibly because HIV epitopes recognized by these alleles are evaded through viral mutation *in vivo* (99,100). The functional basis of *HLA B*35* influence was subsequently shown to reflect allele specific recognition of viral epitopes (100). *HLA-B*35*-encoded molecules comprise a serologically defined group of closely related allele products that display two distinct peptide recognition specificities. *HLA-B*35-PY* molecules recognize processed nine-amino acid long HIV peptides with proline in position 2 with tyrosine in position 9; *HLA-B*35-Px* molecules present peptides with proline in position 2 and a variety of non-tyrosine amino acids in position 9 (101). Population genetic-based survival association analysis revealed the entire *B*35*-mediated AIDS acceleration was caused by *B*35-Px* alone, since *B*35-Py* carriers progress on average like individuals without any *HLA-B35* alleles (100). An interesting retrospective distinction is that *B-35-Px* alleles in Caucasians (*B*3202*, *B3503*, *B3504* and low level *B*5301*) are actually distinct allele transcripts from

Table 3. AIDS restriction genes: comparison of effects between African and European Americans

	Allele or factor	Gene function	Mutation or variant allele effect	Effect	Relative risk or hazard[a]		References
					AA	EA	
Protective factors							
CCR5	Δ32	HIV-1 coreceptor	Limits HIV-1 cell entry	HIV-1 infection resistance	NA	0.03	(54)
				Delays AIDS	NA	0.38	(54)
CCR2	64I	HIV-1 coreceptor	Blocks dimerization of receptor with CXCR4?	Delays AIDS	1.12	0.69	(58)
SDF1	3′A	CXCR4 ligand	Unknown	Delays AIDS	NA	0.36	(47)
CXCR6	E3K	CC receptor	Codon change may alter ligand binding efficiency	Increased survival time after PCP diagnosis	0.37	NA	(98)
CCRL2	167Y	CC receptor	Codon change may alter ligand binding efficiency	Resistance to PCP in EA	NE	0.32	
MCP1.MCP3. Eotaxin	Hap 7	Immune modifiers	Unknown	HIV-1 Infection resistance	0.6	0.6	(83)
HLA	B*27	Ag presentation	Hinders HIV immune escape	Delays AIDS	NA	0.70	(49)
HLA	B*57	Ag presentation	Hinders HIV immune escape	Delays AIDS	0.31	0.45	(49)
KIR-HLA	KIR3DS1 + HLA Bw4-80I	Receptor and ligand for innate immunity	May aid NK cell action against HIV infected cell	Delays AIDS	0.25	0.59	(100)
Susceptible factors							
IL10	5′A	Th2 cytokine	Down-regulates IL10	Accelerates AIDS	NR	1.44	(76)
				Promotes HIV-1 infection	NR	1.75	(76)
IFNG	179T	Th1 cytokine	Aberrant IFNG regulation	Accelerates CD4 loss, AIDS	2.47	NA	(97)
RANTES	In1.1C	CCR5 ligand	Down-regulates RANTES	Accelerates AIDS	1.93	NE	(79)
	Haplotype R3	CCR5 ligand		Accelerates AIDS	1.70	2.27	(79)
HLA	B*35-Cw*04	Antigen presentation		Accelerates AIDS in EA	NE	2.28	(100)
HLA	B35*Px	Antigen presentation	Weak epitope binding may help HIV immune escape	Accelerates AIDS	2.13	2.69	(100)
CCR5	+.P1.+	HIV-1 coreceptor	Upregulates CCR5 expression	Accelerates AIDS	2.31 (Dom)	1.79 (Rec)	(56,51)
HLA class I	1 locus homozygosity	Antigen presentation	Reduced epitope recognition repertoire	Accelerates AIDS	2.7	1.39	(99)
HLA class I	2 or 3 loci homozygosity	Antigen presentation	Reduced epitope recognition repertoire	Accelerates AIDS	NA	4.33	(99)
KIR3DS1	KIR3DS1 in absence of ligand	Activating receptor for innate immunity	Poor regulation of NK cell activity	Accelerates AIDS	2.23	1.21	(57)

[a]Only one representative RH from three AIDS endpoints (CD4 200, AIDS 1993 or AIDS 1987) assessed is listed.
NA, effective genotype is absent or very rare to assess. NE, no effect; NR, not reported; EA, European Americans; AA, African Americans.

*B*35-Px* alleles found in AA (largely B*5301). Perhaps adaptive retention of *B*35-Px* determinants retained different available alleles on different continents in response to recent disease outbreaks.

The large number of distinctive alleles for *HLA* class I and class II loci has been hypothesized to be maintained by heterozygous advantage since individuals presenting a broad array of antigenic peptides may have a more effective immune response to pathogens. Numerous studies have shown associations between specific *HLA* alleles and disease resistance or susceptibility, particularly for malaria, hepatitis, and HIV-1/AIDS (53,102–104). Recently, evidence for overdominant selection was demonstrated by the effects of one-, two- or three-locus homozygosity at the *HLA* class I loci and progression to AIDS (99). Individuals heterozygous at *HLA*-A, B and C enjoyed longer survival than those homozygous at one or more class I loci. Because of increased diversity at the *HLA* class I loci among AA, more EA were observed to be homozygous at 1 or more *HLA* class I locus. Maximal heterozygosity is presumed to be advantageous and under positive selection since a broader range of pathogenic epitopes can be recognized by specific cytotoxic T cells and the opportunities for escape mutants to arise is limited (105–107).

SUMMARY

Although infectious diseases are seldom viewed as genetic diseases, both malaria and AIDS provide models for the study of complex host–pathogen interactions (12,45). In the case of malaria, the genomic footprints left by centuries of selective pressure from *P. falciparum* and *P. vivax* can be observed by extended haplotype homozygosity, overdominant selection and fixation of resistance alleles. By extension, common alleles that are involved in immune response to other microbial pathogens have also been shaped by countless malaria epidemics that have afflicted isolated populations. The consequences are evident when one considers the highly polymorphic *HLA* class I and class II genes that are fundamental in the mounting of humoral, cell mediated and innate immune responses. Similarly, more emphasis is needed for studies of cytokines and chemokines where modest fluctuations in transcriptional activity influence disease outbreaks, perhaps at the burden of triggering autoimmunity, atopy or inflammatory responses.

The genes encoding the HIV-1 and *P. vivax* receptors CCR5 and DARC, respectively, belong to a large family of paralogous genes that have considerable overlap in function, chemokine binding and protein structure. The resistant alleles to *CCR5* and *DARC* are null mutations providing near-absolute protection against their respective pathogens in the homozygous state, with little adverse phenotype to their carriers. It is interesting to speculate that this genomic redundancy provides an evolutionary mechanism for pathogen avoidance at small cost to the host.

Although the HIV-1 epidemic in humans emerged within the last century and has not yet had time to leave its own adaptive shadow in our genomes, disease gene alleles that provided historic advantage against infectious diseases may today be selectively influenced by the AIDS epidemic. We and others have postulated that a very strong selective force from a deadly pathogen epidemic in historic times may be responsible for the rapid elevation of the *CCR5*-Δ32 allele to a modern frequency of 10–15% in Europe (28–31). Candidate epidemics include bubonic plague, smallpox, anthrax and Ebola-like hemorrhagic virus outbreaks. Mortality from the bubonic plague was estimated to be 25–40% between 1346 and 1352 and 15–20% in the Great Plague pandemic of 1665–1666 with episodic outbreaks in Europe until 1750 when plague disappeared from Europe (30,108). A recent demographic model incorporating temporal patterns and age-dependent mortality from bubonic plague and smallpox suggests that a continuous pressure of small pox, infecting European children under 10 with a 30% mortality rate, might also explain the meteoric rise of *CCR5*-Δ32 in Europeans (30). Regardless of the historical agent for selective pressure for *CCR5*-Δ32, it seems to have been subjected to strong selective pressure in our recent past. Like malaria, the current HIV-1/AIDS epidemic may soon deposit its own footprints in human genomes in the form of rapidly expanding protective haplotypes and selective sweeps of advantageous alleles.

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