0031-3998/09/6505-0055R
PEDIATRIC RESEARCH

Vol. 65, No. 5, Pt 2, 2009
Printed in U.S.A.

Host Genetic Determinants of Human Immunodeficiency Virus Infection and Disease Progression in Children

KUMUD K. SINGH AND STEPHEN A. SPECTOR

Department of Pediatrics, University of California, San Diego, La Jolla, California 92093

ABSTRACT: Increasing data support host genetic factors as an important determinants of human immunodeficiency virus type-1 (HIV-1) susceptibility, mother-to-child transmission (MTCT), and disease progression. Of these genetic mediators, those impacting innate and adaptive immune responses seem to play a critical role in viral infectivity and pathogenesis. During primary infection, CCR5 using virus is predominantly transmitted and polymorphisms that affect the expression of CCR5 alter the risk for MTCT and rate of disease. Chemokines that naturally bind to coreceptors alter infectivity and viral pathogenesis. Additional genes that affect innate immunity including those encoding for MBL2 and those modulating the adaptive immune response including CX_3CR1 and human leukocyte antigen types can significantly modify susceptibility and response to HIV-1 infection. As young children develop, the dependence on certain arms of the immune system varies and can alter the effect of genetic variants. Additionally, host genetic factors may alter the response to antiretrovirals. Finally, because HIV-infected children progress more rapidly than adults and have fewer background cofactors, such as drug use and coinfections, the effects of host factors on HIV-1 disease may be more clearly identified. In this review, we summarize available data on the impact of host genetics on MTCT and disease progression of HIV-infected children. **(*Pediatr Res* 65: 55R–63R, 2009)**

Remarkable progress has been made in the interruption of human immunodeficiency virus type-1 (HIV-1) mother-to-child transmission (MTCT) and treatment for HIV-infected children. However, despite these advances many challenges remain to eliminate MTCT through the safest ways possible and in optimizing antiretroviral therapy for pregnant women and children in developed and developing countries. Infants and children can be particularly susceptible to the long-term effects of antiretroviral exposure. Therefore, approaches that lead to optimal drug exposure with the least potential for toxicity for the individual patient are critical if HIV-infected and -exposed children are to lead healthy and productive lives. Moreover, the recent HIV-1 vaccine failures dramatically demonstrate the need to further understand the interactions between host and virus.

HIV usually uses CD4 and a coreceptor to infect cells. The most common HIV coreceptors are the chemokine receptors CCR5 and CXCR4. Although most primary infections involve viruses that use CCR5 as a coreceptor, CXCR4 using virus is often identified in persons with more advanced disease and is associated with more rapid disease progression. To enter target cells, HIV interacts with the CD4 receptor *via* its gp120 protein, thereby stimulating a conformational change in gp120, which exposes a portion of transmembrane glycoprotein gp41, and allows access of the gp120 V-loop to either CCR5 or CXCR4. Subsequently, a peptide in gp41 causes the fusion of the viral envelope and host cell membrane, and allows the viral capsid to enter the target cell.[1]

Host factors are important determinants of susceptibility and pathogenesis of infectious diseases in children and adults. Identifying genetic variants that influence the response to HIV-1 can provide insights into approaches to predict disease progression, can lead to development of new treatments, and can provide new immunologic targets for vaccine development. In this review, we summarize the available data on the impact of host genetics on MTCT and treatment of HIV-infected children. Where appropriate the differences between findings in children compared with adults are discussed. Additionally, we describe the role a particular variant may play in the control of HIV-1 through innate *vs.* adaptive immunity.

Genetic Variants of Coreceptors and Their Ligands Alter HIV-Related Disease Progression

Host and microbial genetics are important determinants of infection and disease outcome. Viruses subvert the immune system by mimicking cellular genes to gain entry into cells and to avoid immunologic detection. With the identification that HIV-1 uses chemokine receptors for cell binding and entry, variants in genes encoding these receptors and their natural ligands have been shown to modify the risk for infection and disease progression. Several single nucleotide polymorphisms (SNPs) within the CC chemokine receptor 5 (*CCR5*) coding and regulatory region seem to affect HIV-1 disease. For HIV-1 infection of adults and children, *CCR5* is a critical coreceptor modulating perinatal transmission (1–3)

Received November 11, 2008; accepted December 17, 2008.

Correspondence: Stephen A. Spector, M.D., Department of Pediatrics, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0672; e-mail: saspector@ucsd.edu; kusingh@ucsd.edu

This work was supported by Grants from the National Institute of Allergy and Infectious Diseases, The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network (AI-069536).

Abbreviations: APOBEC3G, apolipoprotein B mRNA editing catalytic polypeptide 3G; **CCR2,** chemokine (C-C motif) receptor 2; **CCR5,** chemokine (C-C motif) receptor 5; **CCL3L1,** chemokine (C-C motif) ligand 3-like 1; **CXCR4,** chemokine (C-X-C motif) receptor 4; **CX_3CR1,** chemokine (C-X3-C motif) receptor 1; **HIV-1,** human immunodeficiency virus type-1; **IL4,** interleukin-4; **MBL,** mannose-binding lectin; **MCP-1,** monocyte chemotactic protein-1; **MTCT,** mother-to-child transmission; **SDF-1,** stromal cell-derived factor-1

with a deletion of 32-bp from the coding region of the *CCR5* gene (Δ32) providing almost complete protection against HIV-1 infection in individuals with the homozygous mutant genotype (*CCR5*-Δ32/Δ32) (4–7). Individuals heterozygous for *CCR5*-wt/Δ32 are less likely to be infected with HIV-1 and show a slower rate of disease progression (2,3,5,6,8,9). Several SNPs in the regulatory region of the *CCR5* gene, including a G to A polymorphism at position 59029, a T to C polymorphism at position 59353 and a C to T polymorphism at position 59356 have been reported to alter the rate of disease progression to AIDS (8,10).

A polymorphism in the coding region of the CC chemokine receptor 2 (*CCR2*), a minor HIV-1 coreceptor, at position 180 (G to A polymorphism) leads to expression of an isoleucine replacing a valine at amino acid position 64 (designated as *CCR2*-64I) and has been associated with slower disease progression of HIV-1–infected adults (9,11). Similarly, in the 3′-untranslated region of the gene encoding the CXC chemokine *SDF*-1α, the only natural ligand of the HIV-1 coreceptor *CXCR4*, a G to A polymorphism at position 801 has been reported to delay the rate of disease progression to AIDS in its homozygous (A/A) form in an initial report (12), but not by others (13–15). The *SDF1*-3′-A polymorphism has also been reported to be associated with increased perinatal transmission of HIV-1 (16). Some of the studies demonstrating these effects are discussed below and are summarized in Table 1 and Figures. 1 and 2.

In a cohort of over 1000 HIV-infected children, who participated in Pediatric AIDS Clinical Trials Group 152 or 300 protocols and received mono- or dual-nucleoside reverse transcriptase inhibitor treatment before the availability of effective antiretroviral therapy, we studied the effects of *CCR2*-V64I, *CCR5*-wt/Δ32, *CCR5*-59029-G/A, *CCR5*-59353-T/C, *CCR5*-59356-C/T and *SDF1*-3′-G/A polymorphisms on the rate of disease progression and neurologic impairment (17). These studies confirmed that the *CCR5*-wt/Δ32 genotype is associated with slower disease progression. HIV-infected children with the *CCR5*-wt/Δ32 genotype at study entry had higher mean $CD4^+$ lymphocyte counts, $CD4^+$ percentages and cognitive scores, and lower plasma HIV-1 RNA levels than those with the wt/wt genotype. Moreover, children with the *CCR5*-wt/Δ32 genotype were less likely to be severely impaired (cognitive index score <70) at baseline or experience central nervous system (CNS) impairment than those with the homozygous wild type. Although there was a clear benefit observed from the *CCR5*-wt/Δ32 genotype, protection was incomplete and some children did experience disease progression in this group. Because HIV-1 coreceptor usage may change over time in a given individual, it is possible that a switch from *CCR5* to *CXCR4* usage, which is associated with accelerated disease progression in adults and children (18–21), may have occurred in some of those who progressed.

Despite the important impact of the *CCR5*-32bp deletion in delaying disease (12% *vs.* 26% of those with and without the 32bp deletion progressed within 2 y), the Δ32 variant occurred in only 6% of the total cohort. In contrast, a genetic variant within the *CCR5* promoter region, 59029-A/A was found in ~25% of HIV-infected children and was associated with an almost 50% increase in disease progression when compared with those with the G/A or G/G genotype. Therefore, on a population basis, the *CCR5*-59029-G/A genetic variants have a greater overall impact on HIV-related disease in children than the *CCR5*-wt/Δ32 variant. Another variant in the *CCR5* promoter region at position 59353-C/T was found to have an almost 40% greater risk for children with the C/C genotype having a cognitive-index score of <70 compared with those with the T allele.

The impact of CCR2 on HIV-related disease remains controversial. Although *CCR2* is recognized as a minor coreceptor for HIV-1 *in vitro*, whether it serves as a coreceptor in humans remains to be clarified. However, several studies in adults have identified that a *CCR2* variant, *CCR2*-64I, alters disease progression (9,11,13). In contrast, we have found no association between disease progression and death with any of the *CCR2* genotypes. The reason(s) for the different effects observed in children *vs.* adults with the *CCR2* variants are unclear. However, it is likely that the alteration in disease progression found in adults results from modulation of the immune response to HIV-1 as related to the binding of CCR2 with its ligand MCP1 (CCL2). It is possible that the broad immaturity of the immune system of young children compared with adults masks any effect this interaction may have on viral control.

The natural ligand for CXCR4, SDF-1, has also been associated with HIV-1 disease in some studies of adults and children. In our own research, children with the *CCR5*-wt/wt genotype and the *SDF1*-3′-A/A variant were more likely to experience disease progression than those with either the G/A or G/G genotypes. These findings are consistent with other studies in children that reported slower disease progression associated with the *SDF1*-3′-A/A genotype (22,23). However, only a small number of individuals within a given population have the *SDF1*-3′-A/A genotype ($<2\%$ in our studies).

A Chemokine Receptor Genetic Variant that Affects Inflammatory Cell Recruitment Alters HIV-1 Disease Progression Independent of $CD4^+$ Lymphocyte Count and HIV-1 RNA Load

Clinical monitoring of infected persons relies on monitoring of $CD4^+$ lymphocyte count and viral load where the plasma HIV-1 RNA predicts that rate of disease progression, whereas the $CD4^+$ count is used as a predictor of the current risk an individual will develop an HIV-related complication. Our studies of the chemokine receptor CX_3CR1 demonstrate how host genetics has the potential to provide additional information about an individual's risk for disease progression and related complications independent of $CD4^+$ count and viral load (24).

CX_3CR1 belongs to a family of G-protein–coupled receptors and is a leukocyte chemotactic and adhesion receptor for fractalkine (25) and may also serve as a minor HIV-1 coreceptor (26,27). Two nonsynonymous polymorphisms in the coding region of the *CX_3CR1* gene were initially identified as possibly being associated with more rapid disease progression in HIV-1–infected adults (28): a "G" to "A"

Table 1. *Effects of host genetic factors reported in HIV-1 infected children*

Gene	Allele	Effects observed	Presumed mechanism of action	References
CCR5	Δ32	Decrease risk of MTCT	Knockout *CCR5* expression	17
	Δ32	Delay disease progression and decrease CNS	Decrease available CCR5	17
CCR5	59029A	Accelerate disease progression	Increase *CCR5* expression	17
CCR2	64I	No effect	Interact with and reduce CXCR4	17
CCL3L1	Copy number variation	Lower copy numbers accelerate disease progression	Low copy numbers decrease CCL3L1 expression levels	54
CCL3L1	Copy number variation	Lower copy numbers affect HIV mother-to-child-transmission	Low copy numbers decrease CCL3L1 expression levels	46
CXCL12 (SDF-1)	3′A	Accelerate disease progression	Impede CCR5-CXCR4 transition (?)	17
CCL2 (MCP-1)	-2518-G	No effect	Stimulate immune response (?)	78
CX3CR1	249I	Accelerate disease progression	Impedes immune response (?)	24
	V249 T280	Delays disease progression	Enhance immune response (?)	24
IL-4	-589T	No significant effect	Increase IL-4 expression, enhances immune response	76
MBL-2	A/B/C/D or A/O	Enhance infection accelerate AIDS	Decrease MBL expression, incorrect assembly makes protein vulnerable to degradation by metalloproteinases	61
	H/L, X/Y	Enhance infection accelerate AIDS	Genetic variant at promoter positions, decrease MBL expression	61
	P/Q	Enhance infection accelerate AIDS	Genetic variant at 5′ untranslated region, decrease MBL expression	61
APOBEC3G	H186R	Accelerate HIV disease and CNS impairment	Changes histidine to arginine (CAC-CGC) at 186 amino acid position in exon 4	(Singh & Spector) Presented, 16th Congress on Retroviruses & Opportunistic infections, Feb 8–11, 2009, Montreal, Canada
	F119F	Accelerate HIV disease and CNS impairment	Changes TTC-TTT, but no change for phenylalanine at 119 amino acid position	
HLA class I	Maternal HLA homozygosity and mother–child HLA concordance	Increase the risk of vertical transmission of HIV-1	Increased risk may be due to reduced alloimmunity or less diverse protective immune responses	69, 70
HLA class I	Homozygous *HLA*-B or -C alleles	More rapid disease progression	Loss of heterozygous advantage, hence lesser variety of antigenic peptides to T cells and weaker response to HIV epitopes	(Singh & Spector) Presented, 16th Congress on Retroviruses & Opportunistic Infections, Feb 8–11, 2009, Montreal, Canada
	B*27	Slower disease progression	Immunodominant CTL responses to the HIV peptides	
	B*57	Slower disease progression	Restriction of virus replication	
HLA class II	DQB1*2	Protect against HIV-1 disease progression and CNS impairment	Effective $CD4^+$ lymphocyte mediated immune response against HIV	(Singh & Spector) Presented, 16th Congress on Retroviruses & Opportunistic Infections, Feb 8–11, 2009, Montreal, Canada

polymorphism at nucleotide position 745 changes a valine to isoleucine at amino acid position 249 (V/I249) in the sixth transmembrane domain and a "C" to "T" polymorphism at nucleotide position 849 changes a threonine to methionine at amino acid 280 (T/M280) in the seventh transmembrane domain of CX_3CR1 protein. Faure *et al.* (29) reported that HIV-1–infected persons homozygous for *CX_3CR1*-M280 progress to AIDS more rapidly than those with other genotypes. In another study, Brumme *et al.* (30) found a trend toward an association of the I249-T280 and

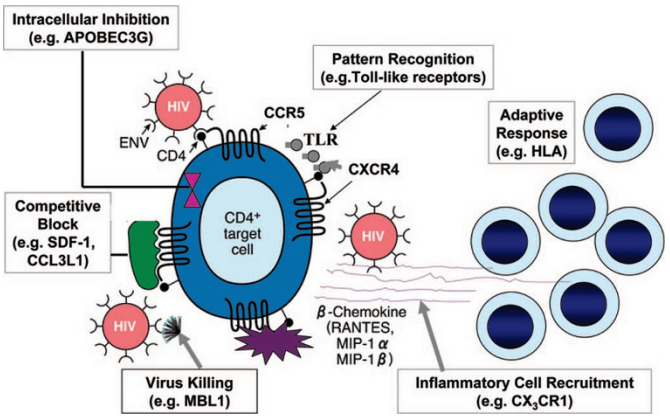

Figure 1. Points where genetics can affect innate and adaptive immunity, and alter HIV-1–related disease progression.

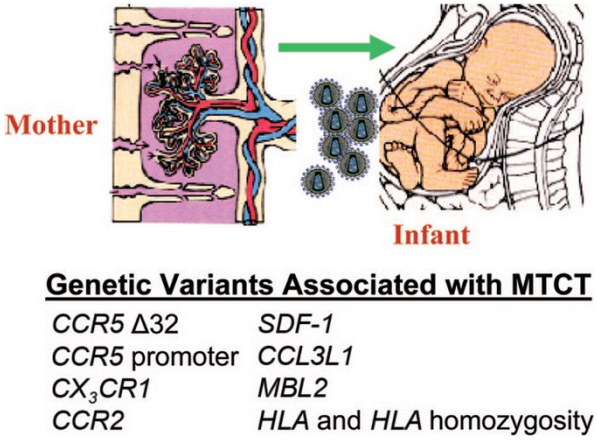

Figure 2. Genetic variants identified to alter HIV-1 mother-to-child transmission. Examples include *CCR5* Δ32, *CCR5* promoter, *CX3CR1*, *CCR2*, *SDF-1*, *CCL3L1*, *MBL2*, *HLA*, and *HLA* concordance. Figure adapted from Spector SA, J Clin Invest 107:267–269, Copyright © 2001, The American Society for Clinical Investigation, with permission.

I249-M280 haplotypes with early immunologic failure in HIV-1–infected adults.

The expression of CX_3CR1 and its ligand, fractalkine, are increased during HIV-1 infection and are reduced on treatment with effective active antiretroviral therapy suggesting that they are important in directing the immune response against HIV-1 (31). Fractalkine expression has been reported to be up-regulated in the brains of patients with AIDS and may be important in HIV-1–associated dementia by regulating the trafficking of monocytes in brain parenchyma (32–34). In addition, fractalkine and CX_3CR1 are expressed in human neurons and glial cells (35). Our findings in HIV-infected children strongly indicate that genetic variants that alter the expression of functional CX_3CR1 can profoundly influence the risk and rate of disease. Moreover, in multivariate analyses, a specific *CX_3CR1* genotype and haplotype strongly predicted both disease progression and CNS impairment independent of markers including $CD4^+$ lymphocytes and plasma HIV-1 RNA load or *CCR5*-wt/Δ32, *CCR5*-59029-G/A and *CX_3CR1*-T/M280 polymorphisms. Children with the wild-type V/V249 genotype that has been associated with greater binding to fractalkine when compared with the I/I249 genotype (28), experienced slower disease progression than children with the I/I249 genotype; however, the disease progression in V/I249 heterozygotes was similar to those with V/V249 genotype. For children with the *CCR5*-wt/wt genotype, we observed a significant association between the presence of the I/I249 genotype and an increased risk for impaired cognition. The same trend of increased risk was observed for children with the M/M280 genotype, albeit with a small number of children. Therefore, it would appear that genetic variants resulting in less CX_3CR1 may place HIV-1–infected children at increased risk for CNS impairment.

Chemokine Receptor Genetic Variants Affect HIV-1 MTCT in the Absence of Antiretrovirals and Perinatal Antiretrovirals that Provide Partial Viral Suppression

Although much progress has been made in the development and implementation of strategies designed to interrupt MTCT, many women in developing countries still have limited access to antiretrovirals (Table 1 and Fig. 2). The identification of genetic markers linked with transmission can help to define risk factors associated with MTCT and provide new insights into HIV-1 pathogenesis that can help in the development of an effective HIV-1 vaccine.

MTCT occurs predominantly with macrophage-tropic (M-tropic), non—syncytium-inducing viruses that use CCR5 as a coreceptor (36), and up-regulation of CCR5 expression in the placenta is associated with vertical transmission (37). A decrease in CCR5 expression could negatively affect immunologic function in newborns and alter the risk of MTCT (38). Moreover, the 32-bp *CCR5* deletion is absent in most African populations (39). Hence, other genetic variants that modify the expression or function of CCR5 or other HIV-1 coreceptors or modulators of innate immunity might alter the risk of MTCT. We examined the impact of *CCR5* promoter, *CCR2*, *CX_3CR1,* and *SDF-1* polymorphisms on the risk of HIV-1 MTCT in three sub-Saharan African cohorts of infants. The study subjects were from Malawi, South Africa, and Uganda. The Malawi and South Africa cohorts consisted of antiretroviral naïve pregnant women and their infants who were involved in vitamin A intervention trials that proved unsuccessful in reducing MTCT (40–42). For the Uganda cohort (HIVNET 012), mothers and their infants were randomly assigned to receive nevirapine or zidovudine (43). Nevirapine given to mother and baby significantly reduced MTCT compared with the zidovudine intervention. Overall, 21.4% of infants were determined to be HIV-1 infected, 20.2% of infants from Malawi, 24.7% from South Africa, and 19.8% from Uganda.

Our findings established a link between *CCR5* promoter variants at positions 59029 and 59353 in infants and the risk for perinatal infection (44). Antiretroviral naïve infants with the 59029-A allele had a higher risk of MTCT *vs.* G/G infants. Exposure to antiretrovirals modified the impact of these genetic variants on MTCT. Children with the *CCR5*-59029-A allele, which has been associated with higher expression of CCR5, were less likely to be infected when exposed to nevirapine (45). However, this same variant was associated with a higher risk for MTCT when zidovudine was given perinatally. Because *CCR5*-59029 and -59353 are in linkage

disequilibrium, the associations between each of these polymorphisms and risk of transmission were similar. We speculate that the difference observed for MTCT between nevirapine and zidovudine exposed mother–infant pairs relates to the long half-life of nevirapine and its ability to rapidly decrease viral load. The effect of zidovudine on viral load was likely less than that of nevirapine and combined with its shorter half-life resulted in similar associations for zidovudine-treated mother–infant pairs as for antiretroviral naïve infants. An alternative explanation for the effects observed with nevirapine and zidovudine on MTCT could be an unidentified differential modulation of the expression of chemokines or chemokine receptors that alter the risk for transmission or effect of other genetic factors (46,47). A recent study reported the potential protective effects of CCR5-59029-G and -59356-T alleles against MTCT in Malawi children with lower maternal viral load (8,48); however, this effect was lost in children with higher maternal viral load.

For the *CCR5*-59356-C/T promoter variant, infants with the T allele had a lower rate of transmission than infants with the C/C genotype. These findings differ from those of Kostrikis *et al.* (8) who reported that the presence of the T/T genotype was associated with a higher rate of MTCT in untreated mother–infant pairs in the United States. Although this may reflect geographic differences (Kostrikis *et al.* evaluated mother–infant pairs from the United States, whereas we studied the children from sub-Saharan Africa), this seems unlikely to be the explanation. Of interest, in a smaller cohort of Kenyan infants, John *et al.* (49) also found a trend toward decreased transmission associated with the 59656-T allele.

No significant effect of *CX_3CR1* genotypes on MTCT was observed in antiretroviral naïve mother–infant pairs. However, antiretroviral-exposed infants carrying the *CX_3CR1*-745-A allele had a significantly higher rate of early transmission compared with infants with the G/G genotype that did not differ with nevirapine and zidovudine exposure.

Mangano *et al.* (50) observed protective effects of *CCR2*-A/A genotype in Argentinean children born to HIV-1–infected mothers, whereas Teglas *et al.* (51) and Brouwer *et al.* (52) failed to find any impact of the *CCR2* genotype on perinatal transmission in France and Western Kenya, respectively. In our study, the *CCR2*-A/A genotype was associated with higher risk of transmission *vs.* G allele carriers suggesting a modest effect of *CCR2* genotypes on MTCT in mother–infant pairs in sub-Saharan Africa.

The presence of *SDF-1*-G/A genotype in mothers was found to be associated with increased perinatal transmission of HIV-1 in Kenya in an earlier study (16). In our own studies, the presence of the *SDF-1*-A allele in infants was rare and no impact on MTCT could be identified. It is likely that if *SDF-1*-A alters MTCT that the relatively low frequency limits its impact on a population basis.

Segmental Duplications in Critical CCR5 Ligand Genes Can Alter HIV-1 Susceptibility and Disease Progression

Much data support a role for the CC chemokines CCL3 [macrophage inflammatory protein (MIP)-1α], CCL4 (MIP-1β), and CCL5 (RANTES) in HIV-1 pathogenesis. In addition to chemotaxis, CC chemokines also play an important role in T-cell activation and in directing and enhancing adaptive immune responses. In humans, CCL3 protein is encoded by two functional genes (*CCL3/LD78*α and *CCL3L1/LD78*β), occurring as two copies and as variable copy numbers, respectively, in different individuals (53). CCL3 may mediate its protective effects through its ability to enhance adaptive immune responses. Research by Gonzalez *et al.* (54) has shown that segmental duplications containing the gene encoding CCL3L1, a potent agonist and HIV-suppressive ligand for CCR5, is associated with variable chemokine expression, and risk of acquiring HIV and rates of disease progression. Of note, they identified that the number of *CCL3L1* copies (gene dose) within a given population may vary and the risk of infection and rate of disease progression is dependent on the relative number of gene copies compared with the mean background for a given ethnic group. Meddows-Taylor *et al.* (55) identified a complex association between *CCL3L1* copy numbers and MTCT. Infants born to HIV-infected mothers with lower levels of CCL3 production were at increased risk of infection and similarly, mothers who transmitted virus had low levels of CCL3. They also suggest that ". . . all *CCL3L1* gene copies are not created equal. . . " and that some duplications may not be as functional as others. In an extension of this group's research, Kuhn *et al.* (46) demonstrated a copy number-dependent relationship between *CCL3L1* gene duplication and MTCT in a cohort from South Africa. In this study, the mean number of copies per diploid genome was 4–5 with infants having fewer copies at greatest risk of infection and those with higher numbers at least risk.

Strength of Innate Immunity Genetic Associations with HIV-1 Disease may Change with Age of Child

As the immune system of children matures, changes occur in how both innate and adaptive immunity respond to microorganisms. Mannose-binding lectin (MBL) protein, encoded by the *MBL2* gene, is an important determinant of the innate immune response during infection (56–59). MBL is an acute-phase protein that is synthesized by the liver and released into the bloodstream where it binds to the mannose residues present on some bacteria, yeast, viruses, and parasites. Binding activates the lectin complement pathway and production of C3b protein *via* MBL-associated serine proteases results in opsonization of pathogens, chemotaxis, activation of leukocytes, and direct pathogen killing (60). The *MBL2* gene encodes 32 kDa subunits which further associate to form high-molecular weight (MW) MBL oligomers (60). *MBL2* variants at the following nucleotide positions affect MBL levels: two SNPs at promoter positions -550-G/C (*H/L* variant) and -221-G/C (*X/Y* variant); one in the 5′ untranslated region + 4-C/T (*P/Q* variant) and three genetic variants at codons 52, 54, and 57 in exon 1, at nucleotide positions 223-C/T (Arg52Cys, *A/D* allele), 230-G/A (Gly54Asp, *A/B* allele), and 239-G/A (Gly57Glu, *A/C* allele), respectively. *MBL2* exon 1 variants result in single amino acid changes affecting oligomerization of MBL. Homozygous wt (*A/A*) sera

contain predominantly fully functional MBL whereas homozygous mutant sera (any combination of *B, C,* or *D* allele) contain mostly low MW MBL.

MBL deficiency has been identified as the cause of common opsonic defect of children. Additional studies have suggested that MBL plays a particularly important role in control of microorganisms in children aged 6–24 mo when maternal IgG levels have waned and the infant's own adaptive immune response is immature (56). Our studies in HIV-infected children indicate that the presence of the *MBL2-O/O* genotype that results in lower expression of MBL protein and impaired innate immunity is associated with more rapid development of CNS impairment in children (61). Similar to earlier studies of the association of *MBL2* in HIV-1–infected adults (62–64), we observed an overall trend for a more rapid disease progression in children with variant *MBL2* genotypes. However most strikingly, we observed significant associations between *MBL2* variants and disease progression including cognitive impairment in children below 2 y of age. These findings are consistent with a critical role for MBL in the immune response of young children (65,66). MBL deficiency has also been associated with increased HIV-1 vertical transmission (62), which emphasizes its important role in controlling HIV-1 infection in young infants and children.

Human Leukocyte Antigen Genotypes Alter MTCT and Rate of Disease Progression

Human leukocyte antigen (*HLA*) class I and class II alleles are the most polymorphic genes in humans and play a fundamental role in acquired immune responses. *HLA* types were among the first genetic markers found to alter the risk of becoming infected with HIV-1 and subsequent rate of disease progression (67,68). Recently, in a case-cohort study of 572 HIV-infected children from Pediatric AIDS Clinical Trials Group 152 and 300, we assessed the impact of *HLA* class I and II alleles on HIV-related disease progression. Our preliminary findings have demonstrated that the presence of homozygous *HLA*-B or C alleles was associated with more rapid disease progression (Singh and Spector, unpublished). In contrast, the presence of B*27 or B*57 alleles was associated with slower disease progression which remained significant after adjustment for race, gender, age, and baseline HIV-1 log RNA, $CD4^+$ count and percent and weight for age z score or other genetic variants including *CCR5*-wt/Δ32, -59029-G/A, *CCR2*-wt/64I, *CX_3CR1*-249-V/I, -280-T/M, *SDF-1*-180-G/A, *MCP-1*-G/A, *MBL2*-A/O, *MBL2*-X/Y, *MBL2*-P/Q, and *MBL2*-H/L. Additionally, the Cw-2 allele protected against disease progression and the A-24 allele was associated with more rapid CNS impairment. For *HLA* class II, the presence of the DQB1*2 allele protected against HIV-1 disease progression and CNS impairment.

HLA has also been found to play an important role in MTCT. *HLA* concordance between a mother and her infant is associated with increased risk of transmission, while *HLA* discordance decreases the risk of MTCT (69,70). Additionally, *HLA* class I homozygosity has been associated with more rapid disease progression (67,68). Children homozygous or who have the same *HLA* class I alleles at both sites with their mothers at one of more *HLA* locus are at increased risk for more rapid disease progression (71).

An Intracellular Antiviral Host Factor Affects HIV Disease

A new class of host restriction factors has been found to play an important role in restricting intracellular viral replication. APOBEC3G (Apolipoprotein B mRNA editing catalytic polypeptide 3G) formerly known as CEM15, is an endogenous inhibitor of HIV-1 replication (72). During permissive infection, APOBEC3G is incorporated into nascent virus particles and mediates deoxycytidine-to-deoxyuridine deamination of minus (first)-strand reverse transcripts in target cells. This results in guanine-to-adenine hypermutation of the viral plus (sense) coding strand and is associated with premature cDNA degradation. Thus, APOBEC3G limits the spread of HIV-1 infection by packaging into the virus during assembly. The potent antiviral activity of APOBEC3G is successfully neutralized by wild-type HIV-1 through vif by mediating its polyubiquitination and rapid degradation through the proteasome (73).

The importance of APOBEC3G-mediated antiviral response against HIV-1 is underscored by the existence of *APOBEC3G* genetic variants influencing disease progression. An *APOBEC3G* variant containing a nonsynonymous substitution of Arg for His at amino acid position 186 is present in African Americans and is strongly associated with more rapid decline of $CD4^+$ T cells and accelerated progression to AIDS (73). Our preliminary studies (Singh and Spector, unpublished) in a cohort of more than 1000 children show that while H186R variants are associated with more rapid HIV disease progression, an F119F variant is associated with moderate protection against the HIV disease progression (74).

Other Host Genetic Factors Potentially Affect Pediatric HIV/AIDS

Interleukin-4 (*IL-4*) differentially regulates the two major HIV-1 coreceptors—increasing *CXCR4* and decreasing *CCR5* expression in primary $CD4^+$ T lymphocytes. Homozygosity of a "C" to "T" polymorphism at the 589 nucleotide position in the *IL4* promoter region (*IL4*-589-C/T), has been correlated with increased rates of SI variant acquisition in HIV-1–infected individuals in Japan (75). We examined the impact of *IL4*-589-C/T polymorphisms on HIV-1 disease in children. To our surprise, we found no association between the *IL4-589*-T allele and disease progression in any analyses performed (76). It is possible that the *IL4-589*-T allele may be in linkage disequilibrium with another allele not discovered so far, which affects disease progression in HIV-1–infected individuals. To date, however, no data exist to support a role for IL4 in HIV-1 disease of children.

Recently, the monocyte chemotactic protein-1 (*MCP-1*)-2518-G allele (associated with higher expression of MCP-1 than wild-type 2518-A allele) has been shown to be associated with HIV-1–related disease (77). We hypothesized that if *CCR2* (MCP-1 receptor) or *MCP-1* variants were important in

HIV-1 pathogenesis in children then combined *CCR2-MCP-1* genotypes would be more likely to demonstrate such an effect than *CCR2* alone. We found that the association of *MCP-1-2518-G/G* genotype with neurocognitive impairment at study entry was marginally significant (78). However, the presence of the *MCP-1-2518-G* allele independently or in combination with *CCR2*-64I allele did not impact overall progression of HIV-1 disease in children.

Several other host genetic factors affecting innate and adaptive immune responses can affect HIV-1 disease in children. These include *apolipoprotein E*, *toll-like receptors*, *DC-SIGN*, *IL-10*, *IL-6*, *IFN-γ*, *TNF-α*, and *CCR5* ligands *MIP1α*, or *RANTES* among others. Research is in progress examining the impact of these and other genetic variants on MTCT and HIV-1 disease progression in children.

Summary

Much research has established that host genetic factors are important determinants of HIV-1 MTCT and the rate of disease progression in children and adults. However, it is clear that no single genetic variant is a dominant factor in HIV-1 pathogenesis, and the risk for transmission and progressive immunosuppression depends on multiple interactions between virus and host. The judicious use of host genetics, however, has the potential to improve the care and treatment of HIV-infected pregnant women and children. In this regard, we have demonstrated that specific genetic variants are predictive of disease progression independent of a patient's $CD4^+$ lymphocyte count and viral load. Thus, the potential exists to develop a model of genetic variants that can be used as an adjunct to standard monitoring of T-cell subsets and plasma HIV-1 RNA to help guide when to start treatment. Although beyond the scope of this review, genetic variants in *CYP* genes and *ABCB1* have been shown to alter the pharmacokinetics and response to specific antiretrovirals and can be used to optimize treatment of children (79,80). Moreover, the *HLA*-B5701 allele is associated with the hypersensitivity reaction associated with abacavir. Screening for this allele has become standard of care for persons before initiating antiretroviral therapy containing abacavir (81). Perhaps, most importantly studies of host genetics provide new insights into innate and adaptive immunologic mechanisms used to control HIV-1 infection (82,83). These findings can lead to improved understanding of how each arm of the immune system orchestrates an integrated, albeit insufficient, response to viral infections. It is likely that these approaches will lead to novel new strategies for vaccine development. In this regard, we believe that a successful HIV-1 vaccine will come when we are able to "educate" innate immunity such that the virus is controlled before establishing infection. Understanding host–virus interactions will be critical to these potential breakthroughs.

Acknowledgments. The authors acknowledge the outstanding statistical support of Terrence Fenton, Michael Hughes, Ping Ruan and Jie Chen, the technical assistance of Rodney Trout, the many clinical investigators who have allowed us to use specimens and outcome data from their clinical studies, the study participants and their families, the Pediatric AIDS Clinical Trials Group (PACTG) and the International Maternal Perinatal Adolescent Antiretroviral Clinical Trials (IMPAACT) Network.

REFERENCES

1. Buseyne F, Janvier G, Teglas JP, Ivanoff S, Burgard M, Bui E, Mayaux MJ, Blanche S, Rouzioux C, Riviere Y 1998 Impact of heterozygosity for the chemokine receptor CCR5 32-bp-deleted allele on plasma virus load and CD4 T lymphocytes in perinatally human immunodeficiency virus-infected children at 8 years of age. J Infect Dis 178:1019–1023
2. Misrahi M, Teglas JP, N′Go N, Burgard M, Mayaux MJ, Rouzioux C, Delfraissy JF, Blanche S 1998 CCR5 chemokine receptor variant in HIV-1 mother-to-child transmission and disease progression in children. JAMA 279:277–280
3. Shearer WT, Kalish LA, Zimmerman PA 1998 CCR5 HIV-1 vertical transmission. Women and Infants Transmission Study Group. J Acquir Immune Defic Syndr Hum Retrovirol 17:180–181
4. Barroga CF, Raskino C, Fangon MC, Palumbo PE, Baker CJ, Englund JA, Spector SA 2000 The CCR5 Delta 32 allele slows disease progression of human immunodeficiency virus (HIV)-1 infected children receiving antiretroviral treatment. J Infect Dis 182:413–419
5. Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, Goedert JJ, Buchbinder SP, Vittinghoff E, Gomperts E, Donfield S, Vlahov D, Kaslow R, Saah A, Rinaldo C, Detels R, O'Brien SJ 1996 Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Science 273:1856–1862
6. Liu R, Paxton WA, Choe S, Ceradini D, Martin SR, Horuk R, Macdonald ME, Stuhlmann H, Koup RA, Landau NR 1996 Homozygous defect in Hiv-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. Cell 86:367–377
7. Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, Saragosti S, Lapoumeroulie C, Cognaux J, Forceille C, Muyldermans G, Verhofstede C, Burtonboy G, Georges M, Imai T, Rana S, Yi Y, Smyth RJ, Collman RG, Doms RW, Vassart G, Parmentier M 1996 Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 382:722–725
8. Kostrikis LG, Neumann AU, Thomson B, Korber BT, McHardy P, Karanicolas R, Deutsch L, Huang Y, Lew JF, McIntosh K, Pollack H, Borkowsky W, Spiegel HM, Palumbo P, Oleske J, Bardeguez A, Luzuriaga K, Sullivan J, Wolinsky SM, Koup RA, Ho DD, Moore JP 1999 A polymorphism in the regulatory region of the CC-chemokine receptor 5 gene influences perinatal transmission of human immunodeficiency virus type 1 to African-American infants. J Virol 73:10264–10271
9. Kostrikis LG, Huang YX, Moore JP, Wolinsky SM, Zhang LQ, Guo Y, Deutsch L, Phair J, Neumann AU, Ho DD 1998 A chemokine receptor CCR2 allele delays HIV-1 disease progression and is associated with a CCR5 promoter mutation. Nat Med 4:350–353
10. Martin MP, Dean M, Smith MW, Winkler C, Gerrard B, Michael NL, Lee B, Doms RW, Margolick J, Buchbinder S, Goedert JJ, O'Brien TR, Hilgartner MW, Vlahov D, O'Brien SJ, Carrington M 1998 Genetic acceleration of AIDS progression by a promoter variant of CCR5. Science 282:1907–1911
11. Smith MW, Dean M, Carrington M, Winkler C, Huttley GA, Lomb DA, Goedert JJ, O'Brien TR, Jacobson LP, Kaslow R, Buchbinder S, Vittinghoff E, Vlahov D, Hoots K, Hilgartner MW, O'Brien SJ 1997 Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City cohort (SFCC), ALIVE Study. Science 277:959–965
12. Winkler C, Modi W, Smith MW, Nelson GW, Wu XY, Carrington M, Dean M, Honjo T, Tashiro K, Yabe D, Buchbinder S, Vittinghoff E, Goedert JJ, Obrien TR, Jacobson LP, Detels R, Donfield S, Willoughby A, Gomperts E, Vlahov D, Phair J, Obrien SJ 1998 Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant. Science 279:389–393
13. Ioannidis JP, Rosenberg PS, Goedert JJ, Ashton LJ, Benfield TL, Buchbinder SP, Coutinho RA, Eugen-Olsen J, Gallart T, Katzenstein TL, Kostrikis LG, Kuipers H, Louie LG, Mallal SA, Margolick JB, Martinez OP, Meyer L, Michael NL, Operskalski E, Pantaleo G, Rizzardi GP, Schuitemaker H, Sheppard HW, Stewart GJ, Theodorou ID, Ullum H, Vicenzi E, Vlahov D, Wilkinson D, Workman C, Zagury JF, O'Brien TR 2001 Effects of CCR5-Delta32, CCR2-64I, and SDF-1 3′A alleles on HIV-1 disease progression: an international meta-analysis of individual-patient data. Ann Intern Med 135:782–795
14. Meyer L, Magierowska M, Hubert JB, Theodorou I, van Rij R, Prins M, de Roda Husman AM, Coutinho R, Schuitemaker H 1999 CC-chemokine receptor variants, SDF-1 polymorphism, and disease progression in 720 HIV-infected patients. SEROCO Cohort. Amsterdam Cohort Studies on AIDS. AIDS 13:624–626
15. van Rij RP, Husman AM, Brouwer M, Goudsmit J, Coutinho RA, Schuitemaker H 1998 Role of CCR2 genotype in the clinical course of syncytium-inducing (SI) or non-SI human immunodeficiency virus type 1 infection and in the time to conversion to SI virus variants. J Infect Dis 178:1806–1811
16. John GC, Rousseau C, Dong T, Rowland-Jones S, Nduati R, Mbori-Ngacha D, Rostron T, Kreiss JK, Richardson BA, Overbaugh J 2000 Maternal SDF1 3′A polymorphism is associated with increased perinatal human immunodeficiency virus type 1 transmission. J Virol 74:5736–5739
17. Singh KK, Barroga CF, Hughes MD, Chen J, Raskino C, McKinney RE, Spector SA 2003 Genetic influence of CCR5, CCR2, and SDF1 variants on human immunode-

ficiency virus 1 (HIV-1)-related disease progression and neurological impairment, in children with symptomatic HIV-1 infection. J Infect Dis 188:1461–1472
18. Bozzette SA, McCutchan JA, Spector SA, Wright B, Richman DD 1993 A cross-sectional comparison of persons with syncytium-inducing and non-syncytium-inducing human immunodeficiency virus. J Infect Dis 168:1374–1379
19. Schuitemaker H, Koot M, Kootstra NA, Dercksen MW, de Goede RE, van Steenwijk RP, Lange JM, Schattenkerk JK, Miedema F, Tersmette M 1992 Biological phenotype of human immunodeficiency virus type 1 clones at different stages of infection: progression of disease is associated with a shift from monocytotropic to T-cell-tropic virus population. J Virol 66:1354–1360
20. Spencer LT, Ogino MT, Dankner WM, Spector SA 1994 Clinical significance of human immunodeficiency virus type 1 phenotypes in infected children. J Infect Dis 169:491–495
21. Tersmette M, de Goede RE, Al BJ, Winkel IN, Gruters RA, Cuypers HT, Huisman HG, Miedema F 1988 Differential syncytium-inducing capacity of human immunodeficiency virus isolates: frequent detection of syncytium-inducing isolates in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. J Virol 62:2026–2032
22. Sei S, Boler AM, Nguyen GT, Stewart SK, Yang QE, Edgerly M, Wood LV, Brouwers P, Venzon DJ 2001 Protective effect of CCR5 delta 32 heterozygosity is restricted by SDF-1 genotype in children with HIV-1 infection. AIDS 15:1343–1352
23. Tresoldi E, Romiti ML, Boniotto M, Crovella S, Salvatori F, Palomba E, Pastore A, Cancrini C, de Martino M, Plebani A, Castelli G, Rossi P, Tovo PA, Amoroso A, Scarlatti G 2002 Prognostic value of the stromal cell-derived factor 1 3′A mutation in pediatric human immunodeficiency virus type 1 infection. J Infect Dis 185:696–700
24. Singh KK, Hughes MD, Chen J, Spector SA 2005 Genetic polymorphisms in CX3CR1 predict HIV-1 disease progression in children independently of CD4+ lymphocyte count and HIV-1 RNA load. J Infect Dis 191:1971–1980
25. Imai T, Hieshima K, Haskell C, Baba M, Nagira M, Nishimura M, Kakizaki M, Takagi S, Nomiyama H, Schall TJ, Yoshie O 1997 Identification and molecular characterization of fractalkine receptor CX3CR1, which mediates both leukocyte migration and adhesion. Cell 91:521–530
26. Combadiere C, Salzwedel K, Smith ED, Tiffany HL, Berger EA, Murphy PM 1998 Identification of CX3CR1. A chemotactic receptor for the human CX3C chemokine fractalkine and a fusion coreceptor for HIV-1. J Biol Chem 273:23799–23804
27. Meucci O, Fatatis A, Simen AA, Miller RJ 2000 Expression of CX3CR1 chemokine receptors on neurons and their role in neuronal survival. Proc Natl Acad Sci USA 97:8075–8080
28. Faure S, Meyer L, Costagliola D, Vaneensberghe C, Genin E, Autran B, Delfraissy JF, McDermott DH, Murphy PM, Debré P, Théodorou I, Combadière C 2000 Rapid progression to AIDS in HIV+ individuals with a structural variant of the chemokine receptor CX3CR1. Science 287:2274–2277
29. Faure S, Meyer L, Genin E, Pellet P, Debre P, Theodorou I, Combadiere C 2003 Deleterious genetic influence of CX3CR1 genotypes on HIV-1 disease progression. J Acquir Immune Defic Syndr 32:335–337
30. Brumme ZL, Dong WW, Chan KJ, Hogg RS, Montaner JS, O'Shaughnessy MV, Harrigan PR 2003 Influence of polymorphisms within the CX3CR1 and MDR-1 genes on initial antiretroviral therapy response. AIDS 17:201–208
31. Foussat A, Bouchet-Delbos L, Berrebi D, Durand-Gasselin I, Coulomb-L'Hermine A, Krzysiek R, Galanaud P, Levy Y, Emilie D 2001 Deregulation of the expression of the fractalkine/fractalkine receptor complex in HIV-1-infected patients. Blood 98:1678–1686
32. Cotter R, Williams C, Ryan L, Erichsen D, Lopez A, Peng H, Zheng J 2002 Fractalkine (CX3CL1) and brain inflammation: implications for HIV-1-associated dementia. J Neurovirol 8:585–598
33. Pereira CF, Middel J, Jansen G, Verhoef J, Nottet HS 2001 Enhanced expression of fractalkine in HIV-1 associated dementia. J Neuroimmunol 115:168–175
34. van der Meer P, Ulrich AM, Gonzalez-Scarano F, Lavi E 2000 Immunohistochemical analysis of CCR2, CCR3, CCR5, and CXCR4 in the human brain: potential mechanisms for HIV dementia. Exp Mol Pathol 69:192–201
35. Hatori K, Nagai A, Heisel R, Ryu JK, Kim SU 2002 Fractalkine and fractalkine receptors in human neurons and glial cells. J Neurosci Res 69:418–426
36. Ometto L, Zanchetta M, Mainardi M, De Salvo GL, Garcia-Rodriguez MC, Gray L, Newell ML, Chieco-Bianchi L, De Rossi A 2000 Co-receptor usage of HIV-1 primary isolates, viral burden, and CCR5 genotype in mother-to-child HIV-1 transmission. AIDS 14:1721–1729
37. Behbahani H, Popek E, Garcia P, Andersson J, Spetz AL, Landay A, Flener Z, Patterson BK 2000 Up-regulation of CCR5 expression in the placenta is associated with human immunodeficiency virus-1 vertical transmission. Am J Pathol 157:1811–1818
38. Ank N, Petersen K, Malmgaard L, Mogensen SC, Paludan SR 2005 Age-dependent role for CCR5 in antiviral host defense against herpes simplex virus type 2. J Virol 79:9831–9841
39. Martinson JJ, Hong L, Karanicolas R, Moore JP, Kostrikis LG 2000 Global distribution of the CCR2-64I/CCR5-59653T HIV-1 disease-protective haplotype. AIDS 14:483–489
40. Semba RD, Miotti PG, Chiphangwi JD, Dallabetta G, Yang LP, Saah A, Hoover D 1998 Maternal vitamin A deficiency and infant mortality in Malawi. J Trop Pediatr 44:232–234
41. Coutsoudis A, Pillay K, Kuhn L, Spooner E, Tsai WY, Coovadia HM 2001 Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. AIDS 15:379–387
42. Coutsoudis A, Pillay K, Spooner E, Kuhn L, Coovadia HM 1999 Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. South African Vitamin A Study group. AIDS 13:1517–1524
43. Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, Jackson JB 1999 Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet 354:795–802
44. Singh KK, Hughes MD, Chen J, Phiri K, Rousseau C, Kuhn L, Coutsoudis A, Jackson JB, Guay LA, Musoke P, Mmiro F, Semba RD, Spector SA 2008 Associations of chemokine receptor polymorphisms with HIV-1 mother-to-child transmission in sub-Saharan Africa: possible modulation of genetic effects by Antiretrovirals. J Acquir Immune Defic Syndr 49:259–265
45. Salkowitz JR, Bruse SE, Meyerson H, Valdez H, Mosier DE, Harding CV, Zimmerman PA, Lederman MM 2003 CCR5 promoter polymorphism determines macrophage CCR5 density and magnitude of HIV-1 propagation in vitro. Clin Immunol 108:234–240
46. Kuhn L, Schramm DB, Donninger S, Meddows-Taylor S, Coovadia AH, Sherman GG, Gray GE, Tiemessen CT 2007 African infants' CCL3 gene copies influence perinatal HIV transmission in the absence of maternal nevirapine. AIDS 21:1753–1761
47. Schramm DB, Kuhn L, Gray GE, Tiemessen CT 2006 In vivo effects of HIV-1 exposure in the presence and absence of single-dose nevirapine on cellular plasma activation markers of infants born to HIV-1-seropositive mothers. J Acquir Immune Defic Syndr 42:545–553
48. Pedersen BR, Kamwendo D, Blood M, Mwapasa V, Molyneux M, North K, Rogerson SJ, Zimmerman P, Meshnick SR 2007 CCR5 haplotypes and mother-to-child HIV transmission in Malawi. PLoS One 2:e838
49. John GC, Bird T, Overbaugh J, Nduati R, Mbori-Ngacha D, Rostron T, Dong T, Kostrikis L, Richardson B, Rowland-Jones SL 2001 CCR5 promoter polymorphisms in a Kenyan perinatal human immunodeficiency virus type 1 cohort: association with increased 2-year maternal mortality. J Infect Dis 184:89–92
50. Mangano A, Prada F, Roldan A, Picchio G, Bologna R, Sen L 1998 Distribution of CCR-5 delta32 allele in Argentinean children at risk of HIV-1 infection: its role in vertical transmission. AIDS 12:109–110
51. Teglas JP, N′Go N, Burgard M, Mayaux MJ, Rouzioux C, Blanche S, Delfraissy JF, Misrahi M 1999 CCR2B-64I chemokine receptor allele and mother-to-child HIV-1 transmission or disease progression in children. French Pediatric HIV Infection Study Group. J Acquir Immune Defic Syndr 22:267–271
52. Brouwer KC, Yang C, Parekh S, Mirel LB, Shi YP, Otieno J, Lal AA, Lal RB 2005 Effect of CCR2 chemokine receptor polymorphism on HIV type 1 mother-to-child transmission and child survival in Western Kenya. AIDS Res Hum Retroviruses 21:358–362
53. Modi WS 2004 CCL3L1 and CCL4L1 chemokine genes are located in a segmental duplication at chromosome 17q12. Genomics 83:735–738
54. Gonzalez E, Kulkarni H, Bolivar H, Mangano A, Sanchez R, Catano G, Nibbs RJ, Freedman BI, Quinones MP, Bamshad MJ, Murthy KK, Rovin BH, Bradley W, Clark RA, Anderson SA, O'Connell RJ, Agan BK, Ahuja SS, Bologna R, Sen L, Dolan MJ, Ahuja SK 2005 The influence of CCL3L1 gene-containing segmental duplications on HIV-1/AIDS susceptibility. Science 307:1434–1440
55. Meddows-Taylor S, Donninger SL, Paximadis M, Schramm DB, Anthony FS, Gray GE, Kuhn L, Tiemessen CT 2006 Reduced ability of newborns to produce CCL3 is associated with increased susceptibility to perinatal human immunodeficiency virus 1 transmission. J Gen Virol 87:2055–2065
56. Dommett RM, Klein N, Turner MW 2006 Mannose-binding lectin in innate immunity: past, present and future. Tissue Antigens 68:193–209
57. Garred P, Larsen F, Madsen HO, Koch C 2003 Mannose-binding lectin deficiency–revisited. Mol Immunol 40:73–84
58. Kilpatrick DC 2002 Mannan-binding lectin: clinical significance and applications. Biochim Biophys Acta 1572:401–413
59. Turner MW 1998 Mannose-binding lectin (MBL) in health and disease. Immunobiology 199:327–339
60. Thiel S, Vorup-Jensen T, Stover CM, Schwaeble W, Laursen SB, Poulsen K, Willis AC, Eggleton P, Hansen S, Holmskov U, Reid KB, Jensenius JC 1997 A second serine protease associated with mannan-binding lectin that activates complement. Nature 386:506–510
61. Singh KK, Lieser A, Ruan PK, Fenton T, Spector SA 2008 An age-dependent association of mannose-binding lectin-2 genetic variants on HIV-1-related disease in children. J Allergy Clin Immunol 122:173–180, 180.e171–172
62. Boniotto M, Crovella S, Pirulli D, Scarlatti G, Spano A, Vatta L, Zezlina S, Tovo PA, Palomba E, Amoroso A 2000 Polymorphisms in the MBL2 promoter correlated with risk of HIV-1 vertical transmission and AIDS progression. Genes Immun 1:346–348
63. Dzwonek A, Novelli V, Bajaj-Elliott M, Turner M, Clapson M, Klein N 2006 Mannose-binding lectin in susceptibility and progression of HIV-1 infection in children. Antivir Ther 11:499–505
64. Garred P, Madsen HO, Balslev U, Hofmann B, Pedersen C, Gerstoft J, Svejgaard A 1997 Susceptibility to HIV infection and progression of AIDS in relation to variant alleles of mannose-binding lectin. Lancet 349:236–240
65. Faber J, Schuessler T, Finn A, Murdoch C, Zenz W, Habermehl P, Meyer CU, Zabel BU, Schmitt H, Zepp F, Knuf M 2007 Age-dependent association of human mannose-binding lectin mutations with susceptibility to invasive meningococcal disease in childhood. Pediatr Infect Dis J 26:243–246
66. Koch A, Melbye M, Sorensen P, Homoe P, Madsen HO, Molbak K, Hansen CH, Andersen LH, Hahn GW, Garred P 2001 Acute respiratory tract infections and mannose-binding lectin insufficiency during early childhood. JAMA 285:1316–1321

67. O'Brien SJ, Gao X, Carrington M 2001 HLA and AIDS: a cautionary tale. Trends Mol Med 7:379–381
68. Carrington M, O'Brien SJ 2003 The influence of HLA genotype on AIDS. Annu Rev Med 54:535–551
69. Mackelprang RD, John-Stewart G, Carrington M, Richardson B, Rowland-Jones S, Gao X, Mbori-Ngacha D, Mabuka J, Lohman-Payne B, Farquhar C 2008 Maternal HLA homozygosity and mother-child HLA concordance increase the risk of vertical transmission of HIV-1. J Infect Dis 197:1156–1161
70. Polycarpou A, Ntais C, Korber BT, Elrich HA, Winchester R, Krogstad P, Wolinsky S, Rostron T, Rowland-Jones SL, Ammann AJ, Ioannidis JP 2002 Association between maternal and infant class I and II HLA alleles and of their concordance with the risk of perinatal HIV type 1 transmission. AIDS Res Hum Retroviruses 18:741–746
71. Kuhn L, Abrams EJ, Palumbo P, Bulterys M, Aga R, Louie L, Hodge T 2004 Maternal versus paternal inheritance of HLA class I alleles among HIV-infected children: consequences for clinical disease progression. AIDS 18:1281–1289
72. Simon JH, Gaddis NC, Fouchier RA, Malim MH 1998 Evidence for a newly discovered cellular anti-HIV-1 phenotype. Nat Med 4:1397–1400
73. Sheehy AM, Gaddis NC, Malim MH 2003 The antiretroviral enzyme APOBEC3G is degraded by the proteasome in response to HIV-1 Vif. Nat Med 9:1404–1407
74. An P, Bleiber G, Duggal P, Nelson G, May M, Mangeat B, Alobwede I, Trono D, Vlahov D, Donfield S, Goedert JJ, Phair J, Buchbinder S, O'Brien SJ, Telenti A, Winkler CA 2004 APOBEC3G genetic variants and their influence on the progression to AIDS. J Virol 78:11070–11076
75. Nakayama EE, Meyer L, Iwamoto A, Persoz A, Nagai Y, Rouzioux C, Delfraissy JF, Debre P, McIlroy D, Theodorou I, Shioda T 2002 Protective effect of interleukin-4-589T polymorphism on human immunodeficiency virus type 1 disease progression: relationship with virus load. J Infect Dis 185:1183–1186
76. Singh KK, Hughes MD, Chen J, Spector SA 2004 Lack of protective effects of Interleukin-4–589-C/T polymorphism against HIV-1-related disease progression and central nervous system impairment, in children. J Infect Dis 189:587–592
77. Gonzalez E, Rovin BH, Sen L, Cooke G, Dhanda R, Mummidi S, Kulkarni H, Bamshad MJ, Telles V, Anderson SA, Walter EA, Stephan KT, Deucher M, Mangano A, Bologna R, Ahuja SS, Dolan MJ, Ahuja SK 2002 HIV-1 infection and AIDS dementia are influenced by a mutant MCP-1 allele linked to increased monocyte infiltration of tissues and MCP-1 levels. Proc Natl Acad Sci USA 99:13795–13800
78. Singh KK, Hughes MD, Chen J, Spector SA 2006 Impact of MCP-1-2518-G allele on the HIV-1 disease of children in the United States. AIDS 20:475–478
79. Saitoh A, Sarles E, Capparelli E, Aweeka F, Kovacs A, Burchett SK, Wiznia A, Nachman S, Fenton T, Spector SA 2007 CYP2B6 genetic variants are associated with nevirapine pharmacokinetics and clinical response in HIV-1-infected children. AIDS 21:2191–2199
80. Saitoh A, Singh KK, Powell CA, Fenton T, Fletcher CV, Brundage R, Starr S, Spector SA 2005 An MDR1-3435 variant is associated with higher plasma nelfinavir levels and more rapid virologic response in HIV-1 infected children. AIDS 19:371–380
81. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jagel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A 2008 HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 358:568–579
82. Blanche S 1994 HIV in infants and children: transmission and progression. In: HIV: Advances in Research and Therapy. Cliggot Communications Greenwich, Connecticut, 4, pp 9–13
83. Spector SA 2001 Mother-to-infant transmission of HIV-1: the placenta fights back. J Clin Invest 107:267–269