In recent years, the sequencing of mammalian and microbial genomes has provided the opportunity to study how genetic variation in the host and pathogen influence the course of infectious disease. In the case of HIV-1 infection, such studies have led to identification of key viral proteins that determine pathogenicity, immune evasion, or drug resistance. In addition, candidate gene association studies have uncovered a large number of host genetic variants that influence the outcome of infection and some organ-specific complications. HIV-associated nephropathy (HIVAN) is a pathologically distinct complication of HIV infection. Interindividual variability in incidence, skewed ethnic distribution, and familial aggregation of HIVAN with other forms of ESRD have suggested genetic susceptibility as a major contributing factor. This article reviews the host genetic factors that influence the course of HIV-1 infection and discusses murine models that have increased the understanding of HIVAN pathogenesis and demonstrated the role of genetic background on determination of disease.


Infectious diseases represent a complex encounter between two organisms with distinct genomes. Whereas the pathogen’s genome has evolved to maximize efficient invasion of the host for perpetuation of its life cycle, the host has evolved defense mechanisms to protect itself from deleterious consequences of infection. The interaction of genetic factors between host and pathogen influences every aspect of infection, from acquisition, resistance, and immune response to disease progression and specific end-organ complications. Genetic determinants of infectious disease have been increasingly clarified in the past few years, largely as a result of our expanded knowledge of the mammalian and microbial genomes as well as major technological advances in molecular genetics. In this review, we discuss the host genetic susceptibility factors that predispose to HIV infection and its complications. We also discuss how such approaches may be used to discover genes that confer susceptibility to HIV-associated nephropathy (HIVAN). Table 1 summarizes the definitions of the common genetic terms used in this review.

### Approaches to Studying Genetic Susceptibility to Infectious Disease

Methodologically, one can study either genetic variations in the pathogen that lead to infectious complications or focus on host genetic susceptibility factors. The sequencing of the HIV genome has improved understanding of the function of specific viral gene products and led to successful identification of genetic variations that enhance pathogenicity. The HIV-1 genome encodes a total of nine genes that are flanked by long terminal repeat sequences that are required for genome integration and regulation. These can be subdivided into genes that encode the major structural proteins \((\text{gag}, \text{pol}, \text{and env})\), the regulatory proteins \((\text{tat} \text{ and rev})\), and the accessory proteins \((\text{vif}, \text{vpr}, \text{vpu}, \text{and nef})\). Their major function and polymorphisms are summarized in Table 2. The rapid replication of the virus coupled with the error-prone viral transcription process results in the generation of many viral mutants in the course of a single infection. As a consequence, HIV virus is able to effectively evade the immune system of the host. Sequencing of variants that develop in the course of HIV-1 infection has provided significant insight into disease pathogenesis. Mutations in the viral peptides that are presented to HLA class I molecules and viral inhibition of HLA I cell surface expression can allow the virus to escape recognition by cytotoxic T cells and NK cells (1,2). Viral antigenic variation and inhibition of HLA class II helps to evade the humoral immunity (2,3). HIV-1 is also able to evolve independently in various tissues, forming latent viral reservoirs that evade immune surveillance and promote organ-specific complications (4). The high mutation rates are also responsible for drug resistance and present a major obstacle for vaccine development.

Approaches for identification of host susceptibility loci fall into two broad categories: linkage approaches and association studies. The linkage approach consists of following of co-segregation of disease with specific markers that can point to chromosomal location of the susceptibility gene. Linkage studies necessitate identification of families with the trait of interest and are best suited for detection of single genes with large effects. The advantage of this approach is the ability to identify novel genes without any previous knowledge about disease pathogenesis. In the nephrology field, the application of the linkage method has enabled identification of many genes underlying Mendelian forms of renal disease (e.g., polycystic kidney disease [5,6], congenital nephrotic syndrome [7], FSGS [8–10]), proving novel insights into disease pathogenesis. However, studying genetic susceptibility to infectious disorders by...
linkage approaches is complicated by the requirement for multi-
plex families. Hence, one would need to identify families that
segregate a genetic susceptibility factor that is unmasked by
exposure of multiple family members to the infectious agent.
Such studies have been carried out for infectious disorders that
are endemic in certain parts of the world, such as tuberculosis
and leprosy. For example, studying South Vietnamese multi-
plex families led to the identification of variants that are shared
between the \textit{PARK2/PARC\textsubscript{G}} genes as genetic susceptibility fac-
tors for leprosy (11,12).

If an infectious disease affects rodents, then one can also
carry out linkage studies in inbred strains. For example, a large
number of well-defined inbred mouse strains can be tested for
susceptibility to infectious diseases of interest. Mice with con-
trasting susceptibility can then be interbred to generate a map-
ing progeny that can identify loci that impart susceptibility to
infectious disease. The power of mouse linkage studies lies in
the possibility to breed mice in large numbers and the ability to
control environmental parameters strictly. Because of these
advantages, one can study complex, multifactorial traits and

In addition, the completion of the genome sequence of the
mouse has greatly facilitated gene identification (15). Given the
large degree of conservation between mammalian genome, it is
likely that genes that are identified in rodent models will point
to biologic pathways that will be relevant to the human situa-
tion. The feasibility of this approach is demonstrated by suc-
cessful identification of genes that mediate susceptibility to
tuberculosis, anthrax, and legionella infections (16–18).

Genetic association studies investigate the impact of genetic
factors on disease by comparing allele frequencies of molecular
variants in case-control cohorts (19,20). Association studies do
not require families and have the potential to address a genetic
basis of sporadic forms of disease. In the candidate gene asso-
ciation studies, a gene that has been implicated in the disease of
interest is surveyed for polymorphisms, which are then geno-
typed in cohorts of patients and healthy control subjects. Now-
adays, array technology permits simultaneous interrogation of
hundreds of thousands of polymorphisms for testing associa-
tion of variants with the disease of interest. Hence, comprehen-
sive genome-wide association studies have become feasible,
lifting the requirement for \textit{a priori} knowledge of disease biology
(21). This approach is best suited for studying multifactorial
traits, which are typically determined by the interplay of mul-
tiple variants that confer small additive effects on the pheno-
type. If case patients and control subjects are well matched,
then one would expect that statistically significant differences
in allele frequency will emerge at true susceptibility loci. Ge-

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Genetic markers} & Short stretches of DNA at known chromosomal locations that differ between 
individuals; the two most commonly used markers are single-nucleotide 
polymorphisms and microsatellites. \\
\hline
\textbf{Linkage analysis} & A method of identifying chromosomal regions that contain disease genes in 
families with the disease of interest. Linkage takes place when a marker is 
located near the trait locus; therefore, marker alleles co-segregate with the trait 
in the family. The probability of joint inheritance depends on the genetic 
distance between the two loci as measured by the recombination fraction. \\
\hline
\textbf{LD\textsuperscript{a} or allelic association} & In population genetics, LD describes the situation whereby alleles at two or more 
loci are observed together more frequently than expected given the known 
allele frequencies and recombination fractions between the loci. LD is usually 
observed at loci that are in close proximity because it takes longer time (more 
generations) to dissipate the ancestral allelic patterns across small 
recombination distances. \\
\hline
\textbf{Penetrance} & The probability that an individual with a given genotype expresses the disease 
phenotype. Reduced or incomplete penetrance implies that not all individuals 
who carry the susceptibility allele will manifest the disease. \\
\hline
\textbf{Genetic heterogeneity} & A situation in which mutations in different genes are responsible for the same 
phenotype in different individuals. \\
\hline
\textbf{Epistasis or gene interaction} & Interaction of two or more alleles at different loci such that the combined effect 
is greater than would be predicted by simply adding the effects of each 
individual allele. \\
\hline
\textbf{Multiplex families} & Families with more than one affected individual. \\
\hline
\textbf{Inbred strain} & An experimental line of animals that are derived by successive brother–sister 
mating to achieve homozygosity across the genome. \\
\hline
\textbf{F1 hybrid} & The first-generation progeny of mating between two different inbred strains; F1 
hybrids derive 50\% of their genome from each parental strain. \\
\hline
\textbf{Backcross} & A cross between an F1 hybrid and one of the parental inbred lines. \\
\hline
\end{tabular}
\caption{Definitions of the selected genetic terms used in the text}
\end{table}

\textsuperscript{a}LD, linkage disequilibrium.
Table 2. HIV-1 viral genes and their products, function, and polymorphisms

<table>
<thead>
<tr>
<th>Viral Genes</th>
<th>Gene Products and Function</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>gag</td>
<td>P55 cleaved by viral protease into four structural proteins: Matrix (p17), capsid (p24), nucleocapsid (p9), and p6</td>
<td>Present in all retroviruses</td>
</tr>
<tr>
<td>pol</td>
<td>Reverse transcriptase, protease, and integrase enzymes</td>
<td>Targets of reverse transcriptase inhibitors and protease inhibitors. Polymorphisms responsible for drug resistance.</td>
</tr>
<tr>
<td>env</td>
<td>Gp160 cleaved by host protease into gp120 and gp41 that are essential for viral cell entry. Gp120 binds with CD4 (HIV receptor) and either CCR5 or CXCR4 (HIV co-receptors). Co-receptor binding is determined by the sequence of V3 variable loop of gp120. The V3 loop is also the principal target for neutralizing antibodies. Gp41 facilitates fusion of viral envelope and cell membrane after binding of gp120 to its receptor and co-receptor; target of fusion inhibitors.</td>
<td>CCR5 is expressed in dendritic cells, macrophages, and T-cells; &quot;M-tropic&quot; HIV variants use the CCR5 co-receptor. CXCR4 is expressed mainly in CD4+ T cells; &quot;T-tropic&quot; HIV variants use CXCR4 co-receptor. gp41 polymorphism affects the intracellular distribution of Env, its incorporation into virions and viral replication capacity. Alterations in gp41 confer resistance to HIV fusion inhibitors.</td>
</tr>
<tr>
<td>tat</td>
<td>Transactivator, binds to the transactivation response element located in the long terminal repeat region of HIV RNA</td>
<td>Potent transcription factor that enhances HIV genome transcription; possible pathogenic role in HIVAN.</td>
</tr>
<tr>
<td>rev</td>
<td>Regulator of viral expression</td>
<td>Facilitates unspliced genomic HIV-1 mRNA translocation from the nucleus to the cytoplasm.</td>
</tr>
<tr>
<td>vpu</td>
<td>Viral protein U</td>
<td>Downregulates CD4 production by inducing its proteolysis, reduces viral cytopathic effect, facilitates the release of new HIV-1 virions from the surface of infected cells; present only in HIV-1.</td>
</tr>
<tr>
<td>vpr</td>
<td>Viral protein R</td>
<td>Transports pre-integrated HIV genome to the nucleus and induces cell-cycle arrest; possible pathogenic role in HIVAN.</td>
</tr>
<tr>
<td>vif</td>
<td>Viral infectivity factor</td>
<td>Affects viral infectivity, counteracts intraviral antiviral factors produced in certain cell types.</td>
</tr>
<tr>
<td>nef</td>
<td>Negative-regulation factor; likely key pathogenic factor in development of AIDS</td>
<td>Augments viral replication and infectivity. Downregulates cell surface CD4 antigen and MHC class I molecules. Downregulates T-cell receptor/CD3 in HIV-2 and simian immunodeficiency virus. This function is protective by maintaining low level of immune activation in infected host and has been lost in HIV-1. Mutations in SH3-binding domain blunt progression to AIDS in transgenic mice. Transgenic mouse models suggest direct pathogenic role in kidney cells.</td>
</tr>
</tbody>
</table>

aHIVAN, HIV-associated nephropathy.
Genetic Susceptibility and HIV

In general, studies of associations between hosts’ susceptibility genes and HIV (summarized in Table 3) have concentrated on two categories of suspects: genes that are involved in the HIV life cycle and genes that are involved in the host’s immune defense. The first category includes polymorphisms in the molecules that HIV uses as co-receptors (variants with different affinities to gp-120) and polymorphisms in their natural ligands (variants that compete with the virus). The best characterized of these traits is a delta 32 mutation in the CCR5 co-receptor discovered in 1996 (25). The homozygotes for a nonfunctional CCR5 have a 32-bp deletion from the coding region that leads to a frameshift mutation. The CCR5-delta32 homozygotes are resistant to infection with macrophage-tropic virus but remain susceptible to infection with T cell–tropic HIV strains, which use CXCR4 for cell entry (26). The heterozygotes have a reduced risk for HIV acquisition and a modest reduction in the rate of disease progression (27). It is interesting that there is a marked racial difference in the frequency of CCR5-delta32 allele, which seems to be much greater among white individuals compared with other ethnic minorities in the United States, including black individuals (27). In addition, several genetic polymorphisms have been identified in the CCR5 promoter region. These may affect HIV transmission or disease progression through effects on the levels of CCR5 expression. For example, an infected host that is homozygous for allele 59029-G within the CCR5 promoter region is less likely to progress to AIDS than a host that is homozygous for the 59029-A allele (28). Another genetic trait, the CCR2-V641 mutation, also seems to affect disease progression (29). Unlike CCR5-delta32 mutation, which is found primarily in white individuals, this mutation was equally frequent in all ethnic groups studied. It is unclear how CCR2 mutation affects disease progression, but it has been suggested that it tracks through linkage disequilibrium with one of the mutations in the promoter region of CCR5 (30).

Although no known variants of CXCR4 are linked with increased HIV susceptibility, a mutation that affects the expression level of its only known ligand, SDF-1, seems to delay AIDS progression (31). SDF-1 has been shown to block in vitro infection with the T lymphocyte–tropic HIV variant. The mutation in the regulatory sequence of SDF-1 leads to upregulation of its synthesis and may result in competitive inhibition of “T-tropic” virus from binding to CXCR4. In a parallel manner, the natural ligands for CCR5 co-receptor (chemokine MIP-1-α, MIP-1-β, and RANTES) have emerged as potential HIV susceptibility factors. Macrophage inflammatory protein-1-αP (MIP-1-αP) is encoded by the CCL3L1 gene, which has undergone several segmental duplications during human evolution. The resulting “copy number” polymorphism has been recently studied in association with the HIV-1 susceptibility in a case-control study. The possession of a low CCL3L1 copy number is associated with a markedly enhanced susceptibility to HIV-1 (32). Comparable to the effect of SDF-1 on T-tropic strains, higher dosages of MIP-1-αP may result in competitive inhibition of M-tropic viruses. Another CCR5 ligand, RANTES, has also been under investigation. In this case, the results are less compelling, but it seems that some RANTES alleles are associated with decreased risk for HIV acquisition and others with accelerated disease progression (33).

Furthermore, HLA genotypes seem to affect AIDS outcomes. By and large, associations between HIV and alleles at class I HLA loci have been observed more frequently than for class II HLA, suggesting that cell-mediated immunity is more effective against HIV than humoral (class II–mediated) immunity. For example, the HLA I allele B*35 has been strongly associated with rapid progression to AIDS (34,35). In contrast, alleles B*57 and B*27 have been associated with long-term nonprogression (36,37). Unfortunately, because of extensive diversity of the HLA alleles, many studies are underpowered to assess accurately the risk that is associated with typically low-frequency HLA variants.

In addition to individual HLA polymorphisms, heterozygosity at all HLA class I loci seems to be protective against AIDS progression (38). The advantage of individuals who are heterozygous at HLA I loci is likely a result of their ability to present a greater variety of antigenic peptides to T cells than homozygotes, resulting in a more productive cellular immune response. Because HLA heterozygosity provides a survival advantage, it seems that a high degree of HLA polymorphism is maintained evolutionarily by selective pressure of continuous exposures to various infectious agents.

Finally, there is recent evidence for a complex gene interaction between specific HLA I alleles and their receptors. For example, the KIR3DS1 gene (killer Ig-like receptor 3) is expressed by NK cells, critical effector cells of the innate antiviral immune response. The gene product recognizes HLA class I molecules on infected target cells and modulates NK activity. Martin et al. (39) found strong evidence of epistatic interaction between HLA-B Bw4-80I allele and KIR3DS1 alleles and showed that joint consideration of these loci is significantly more predictive of disease progression than analysis of each locus separately. KIR gene complex consists of at least 14 genes that are located on chromosome 19q13 and demonstrates significant allelic and haplotype variability. It is interesting that several recent studies correlated outcomes of other viral infections, in particular hepatitis C virus (40) and human papillomavirus (41), with the presence or absence of certain KIR genes in combination with individual HLA alleles.

These examples illustrate genetic factors that confer susceptibility or resistance to primary HIV infection or progression of disease. A similar concept, however, can be applied to organ-specific complications of HIV infection. One may ask, for example, whether there are genes that confer resistance to HIV-related wasting syndrome, HIV-associated neuropathy, HIV dementia, or HIVAN. There are several landmark studies that support this hypothesis for other viral infections. For example, herpes simplex virus-1 infects a large portion of otherwise healthy individuals, but only a minority develop life-threatening HSV-1 encephalitis. The observation that HSV-1 encephalitis clusters in families as well as previous animal studies of IFN signaling pathways permitted the discovery of an encephalitis susceptibility gene that is inherited in an autosomal recessive Mendelian pattern. The defect was present in the intra-
<table>
<thead>
<tr>
<th>Susceptibility Gene</th>
<th>Gene Product and Mechanism</th>
<th>Associated Effect on HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR5-delta 32 deletion</td>
<td>HIV-1 has decreased affinity to mutant CCR5, thereby preventing cell entry of &quot;M-tropic&quot; strains.</td>
<td>Homozygotes have decreased susceptibility to HIV-1 acquisition (25,86). Heterozygosity associated with delayed disease progression (27). In addition, several CCR5 promoter polymorphisms are identified, some associated with delayed disease progression and some with increased risk for HIV transmission (28,87,88).</td>
</tr>
<tr>
<td>CCR5 promoter region polymorphisms</td>
<td>Mutations that affect levels of CCR5 expression. Increased levels theoretically increase susceptibility to HIV infection, whereas decreased levels may confer resistance.</td>
<td>59029-G homozygosity associated with slower disease progression (28). 59356-T homozygosity associated with increased perinatal transmission (88).</td>
</tr>
<tr>
<td>CCR2-V64I mutation</td>
<td>Encodes CCR2. Unknown mechanism. Certain &quot;M-tropic&quot; strains of HIV-1 may be using CCR2 instead of CCR5 for viral entry.</td>
<td>Heterozygosity associated with delayed progression to AIDS (29). May be in LD with a protective polymorphism in the CCR5 regulatory region; its significance is unknown (30).</td>
</tr>
<tr>
<td>SDF-1 regulatory sequence mutation</td>
<td>Increased production of SDF-1, the CXCR4 co-receptor ligand; competitive inhibition of &quot;T-tropic&quot; viral strains</td>
<td>Homozygosity associated with delayed disease progression (31)</td>
</tr>
<tr>
<td>CCL3L1 copy number polymorphism</td>
<td>Increased production of MIP-1-α P, one of the CCR5 co-receptor ligands; competitive inhibition of &quot;M-tropic&quot; viral strains.</td>
<td>Low copy number associated with increased susceptibility to disease acquisition; high copy number protective against infection (32)</td>
</tr>
<tr>
<td>RANTES promoter polymorphism</td>
<td>Altered levels of RANTES (CCR5 ligand) may affect infectivity of &quot;M-tropic&quot; viral strains.</td>
<td>Certain polymorphism associated with decreased risk for HIV acquisition, other with HIV disease progression (33)</td>
</tr>
<tr>
<td>HLA type I (A, B, C) homozygosity</td>
<td>&quot;Heterozygosity advantage&quot;: Homozygotes are able to present a greater variety of antigenic viral peptides to T cells and confer increased resistance or survival. Homozygotes have narrow range of HIV-1 peptides presented to T cells; immune escape occurs more rapidly.</td>
<td>Homozygosity accelerates AIDS; heterozygosity is protective (38).</td>
</tr>
<tr>
<td>HLA type I alleles</td>
<td>Certain HLA I variants present specific viral antigens to CTL more effectively than other variants, generating a stronger and more protective T cell response.</td>
<td>Protective effect: Certain alleles of HLA-B<em>27 and HLA-B</em>57 increased risk: HLA-B<em>35-Px and HLA-Cw</em>04 (although Cw<em>04 seems to be in strong LD with B</em>35-Px) (37).</td>
</tr>
<tr>
<td>HLA type II alleles</td>
<td>Certain HLA II variants may bind with more affinity to key HIV-1 epitopes in conserved regions, thereby improving host’s humoral response and hindering viral escape.</td>
<td>Protective effect: HLA-DRB1*13 (89)</td>
</tr>
<tr>
<td>KIR3DS1 and HLAB Bw4-80I (epistasis)</td>
<td>KIR bind HLA I molecules and modulate NK cell activity. NK cells are critical components of the innate immune system controlling viral infections.</td>
<td>KIR3DS1 allele in combination with HLA-B Bw4-80I genotype is associated with a marked delay in disease progression (39). This is the first model of epistatic gene interaction described for HIV susceptibility.</td>
</tr>
</tbody>
</table>

*CTL, cytotoxic T lymphocyte; KIR, killer Ig-like receptors; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normal T expressed and secreted.
and is thought to be a principal mechanism of glomerulosclerosis with consequent dedifferentiation, proliferation (48). Hence, dysregulation of the glomerular filtration rate markers of proliferation and downregulated markers of glomerular cell loss contribute to podocyte foot process effacement and wrinkling within the collapsed capillary loops, frequently leading to partial capillary lumen occlusions. Electron microscopy demonstrates characteristic glomerular basement membrane folding and wrinkling within the collapsed loops, frequently leading to partial capillary lumen occlusions. Immunohistochemical staining of podocytes reveals upregulated markers of proliferation and downregulated markers of differentiation (48). Hence, dysregulation of the glomerular epithelial phenotype with consequent dedifferentiation, proliferation, and apoptosis leads to loss of glomerular architecture and is thought to be a principal mechanism of glomerulosclerosis in HIVAN.

Data suggest that HIVAN results from direct epithelial infection. Biopsy studies have demonstrated by immunohistochemistry and DNA *in situ* hybridization techniques that a small number of renal epithelial cells harbor HIV-1 (49). These findings have then been confirmed by detection of HIV-1 in tubular cells as well as glomerular visceral and parietal epithelial cells by PCR amplification and RNA *in situ* hybridization (50). It seems that the virus is even capable of active replication and evolution within the renal epithelium (51). These findings suggest that kidney cells not only are infected with HIV-1 but also might constitute a viral reservoir, allowing the virus to undergo slow but productive replication. Nonetheless, the exact process of viral entry into renal tissue remains to be worked out because expression of CD4 and the HIV-1 co-receptors has not been conclusively demonstrated *in vivo*. In one interesting *in vitro* study, HIV-1 quasi-species from the kidney demonstrated differential use of co-receptors (*e.g.*, CXCR4) compared with those that were isolated from the blood, consistent with the notion of renal compartmentalization (52). The presence of CXCR4 on renal epithelial cell line therefore suggests a potential route of entry in renal tubular epithelia.

The epidemiology of HIVAN reveals a strikingly skewed ethnic distribution. Among HIV-infected individuals, almost all cases of HIVAN occur in patients of African descent (53). According to a report from the US Renal Data System, HIVAN had the strongest association with black race of all causes of renal failure among patients who were on maintenance dialysis (47). In addition, among 201 black patients with ESRD that was caused by HIVAN, nearly 25% reported a positive family history of ESRD compared with 6% in a white control group (54). In contrast, HIVAN seems to be very rare in the Asian population (55). This skewed ethnic prevalence has been confirmed in European studies and is not explained by the mode of viral transmission (56,57). Moreover, not all African populations seem to have the same predisposition to HIVAN. A recent screening of 126 Ethiopians who had HIV infection and emigrated to Israel revealed that none of the individuals met clinical criteria for HIVAN, as defined by proteinuria >2 g/d (58). This finding is consistent with known genetic diversity of the African population and clearly demonstrates interpopulation heterogeneity in regard to susceptibility to HIVAN. This notion is further illustrated in a study of South Africans, in which collapsing glomerulopathy was the most common histopathologic entity observed among HIV-positive individuals (59,60).

A significant proportion of HIV-positive black South Africans also presented with an unconventional form of immune complex glomerulopathy, suggesting interindividual variation in susceptibility to classic HIVAN among this population (59). Interindividual variation, racial differences, and familial clustering of kidney disease strongly suggest the existence of HIVAN-specific genetic susceptibility factors that are unmasked in the setting of HIV infection. Although there was an initial suggestion that a polymorphism in the promoter of the Duffy antigen/receptor for chemokines may be involved in susceptibility to HIVAN (61), this has not been confirmed in other studies (62).

Several transgenic animal models of HIVAN have been extremely helpful in formulating the current paradigm of HIVAN pathogenesis. The first model was generated using a noninfectious HIV-1 DNA construct that lacks the *gag* and *pol* genes (63,64). The transgenic Tg26 mouse expressed seven of 15 HIV-1 gene products and developed proteinuria and collapsing FSGS with extensive tubulointerstitial damage that resembles the disease that is seen in humans (64). A similar rat model that
replicates the phenotype of a transgenic mouse has also been developed (65,66). These experiments convincingly demonstrated that the HIV-1 gene products are important in the pathogenesis of HIVAN. Furthermore, when normal kidneys are transplanted into Tg26 transgenic animals, renal lesions do not develop. Conversely, when kidneys that express HIV-1 transgenes are transplanted into wild-type mice, the disease progresses (67). This suggests that local HIV-1 expression in the kidney is required for HIVAN development, and systemic cytokine release with postulated “bystander” renal injury is unlikely to be responsible for the disease.

The generation of transgenic mice with HIV-1 DNA under the control of CD4 gene promoter was achieved in 1998 and resulted in animals with severe AIDS-like illness (68). It is important to note that in this particular model, viral gene products were not expressed in the glomerular epithelium, and, although animals developed severe tubulointerstitial nephritis, the FSGS pattern was not observed. Subsequent introduction of targeted mutations in selected proviral genes in this model revealed that nef was the major determinant of systemic HIV pathogenicity (69), and specific mutations within the nef SH3-binding domain blunted the development of AIDS-like disease (70). Further support for the pathogenic role of Nef in AIDS came from a recently published study by Schindler et al. (71).

The Nef molecule from nonpathogenic strains of simian immunodeficiency virus and HIV-2 induces the downregulation of host T cell receptor/CD3, which seems to be protective through maintaining low levels of immune activation in infected hosts. During viral evolution to HIV-1, Nef supposedly lost this ability, which may partly explain why HIV-1 causes AIDS.

Further animal studies concentrated on dissecting the role of individual viral proteins in pathogenesis of HIVAN. The Nef protein is also highly pathogenic when expressed in kidney cells (57,72,73). The pathogenic role of Nef in the kidney was first described by in vitro experiments, in which podocyte cultures were infected with a series of mutated HIV-1 constructs that had premature stop codons in env, vif, vpr, vpu, nef, tat, or rev gene. It seemed that the nef gene product alone was sufficient to induce podocyte proliferation and dedifferentiation in vitro (72). The transgenic mice with podocyte-specific expression of nef demonstrated similar podocyte dedifferentiation in vivo (57). Surprisingly, these mice did not develop proteinuria or collapsing FSGS pattern on renal biopsy, suggesting that possibly other viral gene products are necessary to acquire the full disease phenotype. In the studies of other transgenic mouse models, Vpr protein emerged as a new nephrotoxic candidate (74). It seems that both vpr and nef can induce mild podocyte injury independently, but, when coexpressed in double transgenic mice, they can act synergistically to produce the FSGS phenotype although without collapsing features (75). The specific interaction between Nef, Vpr, and other viral gene products is under active investigation. Altogether, it seems that viral proteins perturb cell-cycle regulation, a process that eventually results in the dysregulated podocyte phenotype that is observed in HIVAN. Consistent with this notion, amelioration of HIVAN was achieved by inhibition of cyclin-dependent kinases (76). In addition, downstream targets of HIV proteins in the kidney are increasingly identified. For example, He et al. (73) demonstrated that Nef increases Src activity and Stat3 phosphorylation, activating the mitogen-activated protein kinase 1,2 pathways that are implicated in podocyte dedifferentiation. Other investigators have also identified persistent activation of the NF-kB, which results in Fas-mediated apoptosis in renal epithelia (77,78). Genes that are involved in these dysregulated pathways represent good candidates for investigation of polymorphisms that are associated with susceptibility to HIVAN.

As exemplified by genetic studies of tuberculosis and Legionella susceptibility in the mouse, investigation of genetic modifiers among transgenic models may be used to identify genetic factors that mediate susceptibility or resistance to HIVAN. Genetic background has a profound influence on the expression of HIVAN phenotype in one of the best validated models of HIVAN, the aforementioned Tg26 mouse that carries a replication-incompetent proviral HIV-1 transgene (79). These mice were generated on the FVB/N strain background and developed a full-blown HIVAN phenotype (63,64). For assessment of the influence of genetic background on the development of HIVAN, Tg26 mice were outcrossed with five other inbred strains to generate F1 hybrids. Transgenic F1 hybrids, which share 50% of their genome from each parental strain, demonstrated striking variations in renal disease, which were independent of transgene expression levels (79). Two strains, CAST/EiJ and Balb/cJ, were completely protected from renal disease. These data demonstrated that in addition to expression of viral genes, a permissive genetic background is required for manifestation of the HIVAN phenotype. These data may therefore explain the variability in phenotype that is observed among different transgenic models. For example, the absence of overt nephropathy in mice with podocyte-specific expression of the nef gene may be attributable to the genetic background (C57BL/6J) used (57). Consistent with these data, mice that expressed a HIV-1 transgenes in glomerular podocytes developed HIVAN only in the FVB/N but not the C57BL/6J genetic background (80). These genetic modifiers may be identified by intercrossing that is susceptible to resistant strains. Therefore, in an informative mapping cohort between the susceptible Tg26 (FVB/J) and resistant CAST/EiJ strains, a genome-wide analysis of linkage has identified a locus on mouse chromosome 3A1–3 that influences the HIVAN phenotype (named HIVAN1 locus) (79). It is interesting that this locus is syntenic to human chromosome 3q25–27, an interval that shows suggestive evidence of linkage to human diabetic and hypertensive nephropathies (81–84). A review of the HIVAN1 linkage interval revealed many interesting positional candidates related to neoplasia, cell-cycle regulation, and neuronal complications of HIV-1 infection. Because the interval is very large, it will require generation of congenic strains to reduce the linkage region. The HIVAN1 interval explained only 15% of the variance in the renal injury score, suggesting that additional loci with smaller effects account for the remaining variation in disease in the cross studied. This motivated generation of another mapping cohort of HIVAN mice using C57BL/6J as a counterstrain, yielding preliminary evidence of a second HIVAN susceptibility...
ity interval on mouse chromosome 13 (85). These findings have validated the use of mouse models to map genetic modifiers of HIVAN. The presence of multiple loci in mouse models suggests that susceptibility to HIVAN in humans will likely entail interplay between multiple genetic susceptibility factors. The relevance of genes and pathways identified in the mouse model can then be tested in human cohorts with HIVAN. In addition, the ability to perform genome-wide association studies will now enable investigators to study directly genetic susceptibility to HIVAN in humans. It is expected that the integration of information from murine models and human studies will help define pathways that elucidate the pathogenesis of this common HIV-1 complication.

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Disclosures
None.

References


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