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Gene-Gene and Gene-Environment Interactions in HIV-Associated Nephropathy: a Focus on the *MYH9* Nephropathy Susceptibility Gene

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Abstract

Human immunodeficiency virus-associated nephropathy (HIVAN) is a leading cause of end-stage renal disease in African Americans. The HIV-1 virus infects podocytes, cells integral to formation of the glomerular filtration barrier, often leading to focal segmental glomerulosclerosis. HIVAN is typically a complication of late-stage HIV infection, associated with low CD4 cell counts and elevated serum HIV RNA levels. Highly active antiretroviral therapy (HAART) is partially protective and has altered the natural history of HIV-associated kidney disease. Nonetheless, HIVAN remains an important public health concern among HIV-infected African Americans. Although polymorphisms in the *MYH9* gene on chromosome 22 are strongly associated with HIVAN, as well as with idiopathic focal segmental glomerulosclerosis and global glomerulosclerosis (historically labeled "hypertensive nephrosclerosis"), the majority of HIV-infected patients who are genetically at risk from *MYH9* do not appear to develop severe kidney disease. Therefore, we postulate that additional environmental exposures and/or inherited factors are necessary to initiate human HIVAN. Gene-environment interactions have also been proposed as necessary for initiation of HIVAN in murine models. It is important that these novel risk factors be identified, as prevention of environmental exposures and targeting of additional gene products may reduce the risk for HIVAN, even among those harboring two risk alleles in *MYH9*.

Keywords

African Americans; FSGS; HIV-associated nephropathy; kidney disease; *MYH9*

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Introduction

HIVAN was initially described as “acquired immunodeficiency syndrome (AIDS) Nephropathy” in 1984.¹ HIVAN is a common cause of CKD, observed primarily in African Americans (AA).^{2–6} Pathologically, HIVAN is characterized by the collapsing variant of focal segmental glomerulosclerosis (FSGS), with microcystic tubular dilation, tubulointerstitial nephritis, and tubuloreticular inclusions.^{7,8} HIVAN can be a rapidly progressive form of FSGS and is characterized by podocyte proliferation. Patients with pathologically-proven HIVAN demonstrate poorer renal survival relative to HIV-infected individuals with other etiologies of CKD.^{3,9,10} HIV infection and diabetes appear to convey similar risks for kidney disease in AA.¹¹

Epidemiology of HIV-associated nephropathy

The U.S. Renal Data System (USRDS) reported that 0.97% of the 375,152 incident patients initiating chronic dialysis between January 1992 and June 1997 had HIVAN, and 87% were AA.⁶ Four thousand new cases of ESRD were attributed to HIV in the U.S. in 2005,¹² making HIVAN the third leading cause of ESRD in AA between the ages of 20–64 years. The incidence of HIVAN peaked in the U.S. during the mid-1990s¹³ and declined by 50% in the 1998–2001 time period, relative to 1995–1997, in association with the widespread use of HAART.² Although the incidence of HIVAN decreased during the HAART era, its prevalence is now increasing due to the aging of patients as a result of improved survival among those with HIV infection.¹⁴ The true prevalence of HIVAN remains unknown, since the diagnosis requires viral testing and renal histologic analysis; more cases likely exist than are reported. In addition, non-HIVAN causes of kidney disease are often seen in HIV-infected patients, some of which result from HAART.¹⁵ Table 1 summarizes the published incidence and prevalence rates of HIVAN among AA HIV-infected subjects. The prevalence of HIVAN in HIV-infected AA ranges from 3.5% for proteinuria to 12% in postmortem studies.^{16,17} A report in South Africans revealed higher frequencies of HIV immune complex kidney disease (HIVICK), as well as membranous, mesangial hyperplasia, and IgA nephropathy, relative to AA.¹⁸

HIVAN is most often a complication of the late stages of HIV infection, associated with low CD4 cell counts and elevated serum HIV RNA levels.^{2,3,9,10,19–21} However, HIVAN can develop in patients with undetectable viral loads and high CD4 cell counts.^{3,22} Prior history of a low CD4 cell count (ie, nadir CD4 cell count <200 cells/mm³) is a risk factor for HIVAN,⁹ and there is a shorter time to initiation of renal replacement therapy in those with lower CD4 cell counts.³ Prior to the availability of HAART, the prognosis for patients with HIVAN was dismal, and survival was measured in weeks to months.²³ There are several lines of evidence supporting a beneficial role of HIV treatment in improving survival and preserving kidney function, including the negative correlation between CD4 cell count and HIVAN, the decline in the incidence of HIVAN during the HAART era, and case reports of resolution of renal failure after initiation of HAART.^{23–27} Nevertheless, HAART is only partially protective, and many patients with HIVAN ultimately progress to ESRD.^{2,23,28} CD4 cell count restoration using HAART does not correlate with improved renal outcomes,^{10,23} and 65% of patients who progress to ESRD after a diagnosis of HIVAN have had undetectable HIV RNA levels for median durations approaching two years.²³

Pathogenesis of HIVAN

Although HIV-1 viral mRNA and DNA have been detected in renal glomerular and tubular epithelial cells, the mode of HIV-1 viral entry into kidney cells has not been determined.²⁹ Renal epithelial cells lack both CD4 and CD4 co-receptors CXCR4 and CCR5, used by HIV-1 for cellular entry.³⁰ However, expression of CXCR5, an HIV-2 co-receptor, has been

demonstrated on podocytes.³¹ A "renal reservoir" of HIV-1 has been described during primary viral infection.³² Renal biopsies have revealed restoration of the architecture of the renal tubules and resolution of podocyte hypertrophy and glomerular collapse three months after the initiation of antiretroviral therapy. The number of podocytes expressing viral mRNA was unchanged. Similarly, Bruggeman and others observed replication of HIV in renal cells of individuals with HIVAN despite treatment with antiretroviral agents and undetectable serum viral loads.²⁹

Local replication of HIV-1 in renal tubular cells has been confirmed.³³ DNA extracted from renal tubular cells in two patients with HIVAN was used to amplify HIV-1 V3-loop or gp120-envelope sequences. Sequences were compared to the corresponding sequences in monocytes obtained from these same individuals. Sequences obtained from kidney tissue formed tissue-specific subclusters, suggesting local (renal) replication of HIV-1.³³

Normally, podocytes are post-mitotic and do not proliferate. In HIVAN, podocytes appear to de-differentiate and proliferate. Proliferation of de-differentiated podocytes has been proposed as a common mechanism in the development of FSGS and HIVAN.³⁴ Renal biopsy specimens from individuals with FSGS and HIVAN reveal a lack of expression of mature podocyte markers, such as WT-1 (Wilms Tumor-1), CALLA (common acute lymphoblastic leukemia antigen), C3b receptor, GLEPP-1 (glomerular epithelial protein-1), podocalyxin, and synaptopodin.³⁵ While expression of these markers is lost in the collapsed glomeruli of individuals with HIVAN and collapsing FSGS, expression is conserved in other proteinuric renal diseases, such as minimal change disease (MCD) and membranous glomerulonephritis. In addition, staining for the cell cycle protein Ki-67, an indicator of cell proliferation, was observed in renal tissue from HIVAN, but absent in MCD and membranous glomerulonephritis. Similarly, Winston and colleagues reported that Ki-67 staining was present in podocytes and tubular epithelial cells in HIVAN prior to antiretroviral therapy and disappeared during therapy.³²

Expression of HIV in the kidney appears to be necessary for the development of HIVAN, as evidenced by cross-transplantation experiments. Renal transplants were performed between HIV-1 transgenic mice and normal litter mates. The normal kidneys did not develop evidence of HIVAN, while the transgenic kidneys developed nephropathy. This experiment suggests that HIVAN resulted directly from HIV-1 gene expression in the kidney rather than as a result of exposure to circulating virus or other circulating factors.³⁶ Using transgenes encoding the HIV-1 gene products *vpr*, *vif*, *tat*, *rev*, *nef* and *vpu*, Zhong and others observed that transgenic mice expressing HIV-1 selectively in podocytes developed proteinuria and collapsing FSGS with microcystic tubular dilation consistent with HIVAN.³⁷

Of the nine genes encoded by HIV-1, *nef* and *vpr* have been implicated in HIVAN. By creating HIV-transgenic mice with mutations in *vpr*, *nef*, or both sequences, Dickie and associates found that proteinuria and focal glomerulosclerosis only developed in mice with an intact *vpr* gene, while mice with mutated *nef* had less severe disease.³⁸ The findings show a fundamental role for *vpr* in induction of HIVAN and are consistent with other studies revealing interactions between *nef* and *vpr*.³⁹ Expression of *vpr* in cultured renal tubule epithelial cells impairs cytokinesis, leading to cell enlargement and multinucleation.³⁷ Genetic backgrounds are important in the susceptibility to podocyte injury. In the experiments by Zuo and colleagues and Zhong and others, the transgenic lines developed podocyte injury on FVB/N genetic backgrounds, but not on C57BL/6 backgrounds.^{37,39}

Nef is also involved in the pathogenesis of HIVAN. Using podocytes infected with constructs containing premature stop codons in HIV-1 *env*, *vif*, *vpr*, *vpu*, *nef*, or *rev* genes, podocyte proliferation and anchorage-independent growth were seen in all of the constructs except those

containing the *nef* deletion.⁴⁰ HIV-1 *nef* has been shown to result in proliferation of podocytes and decreased expression of synaptopodin and CALLA.⁴¹ Expression of *nef* in podocytes resulted in loss of staining for synaptopodin and WT-1 and expression of the proliferation markers Ki-67 and phosphor-Stat3.⁴² Infection with *nef* also triggers pathways involved in inflammation, altering the actin cytoskeleton. Infection of podocytes with *nef* resulted in increased Src kinase activity and phosphorylation of Stat3, a signaling pathway necessary for cell proliferation. *Nef* induced MAPK1,2 (mitogen-activated protein kinase-1,2) phosphorylation in podocytes both *in vitro* and *in vivo*.⁴³ Lu and others demonstrated that infection with HIV-1 *nef* resulted in changes in the actin cytoskeleton and podocyte effacement *in vitro*. Actin stress fibers form as a result of activation of Rho and lamellipodia form as a result of activation of Rac. *Nef* was found to inhibit RhoA activity and increase activity of Rac1 via Src-induced phosphorylation of Diaphenous interacting protein, p190RhoGAP and vav2.⁴⁴

Genetic factors in human HIVAN

The association of HIVAN with AA ethnicity was recognized in multiple early studies.^{2-4, 6, 45} Among HIV-infected patients, AA had a 31-fold higher risk of ESRD compared to European Americans (EA).¹⁴ The association with African ancestry has also been reported in Europe and Africa.^{19, 20, 46-48}

African Americans have disproportionate risks of several common etiologies of CKD, including FSGS and the distinct collapsing form of FSGS as seen in HIVAN. While these findings suggested a genetic basis, many attributed this risk to ethnic differences in socioeconomic status and lifestyle. In the late 1990's, we demonstrated marked familial aggregation of HIVAN in AA,²⁸ and these patients often had close relatives with ESRD lacking HIV infection. Kidney failure in these relatives was typically attributed to essential hypertension, diabetes, or idiopathic FSGS.⁴⁹ The clustering of disparate forms of ESRD in AA families suggested the existence of overarching "renal failure susceptibility genes," genes independent of the systemic processes of HIV infection, hyperglycemia, or hypertension.⁵⁰

It has since been shown that polymorphisms in the *MYH9* gene are strongly associated with HIVAN in AA, as well as with idiopathic FSGS and clinically diagnosed "hypertension-associated" ESRD (global glomerulosclerosis).⁵¹⁻⁵³ *MYH9* encodes non-muscle myosin heavy chain IIA and is expressed in the glomerular podocyte. The population attributable risk for HIVAN in AA related to *MYH9* is 79%, with an odds ratio of 5.⁵¹ Population attributable risk reflects the percentage of disease that would disappear if the risk allele were replaced by neutral alleles. In this case, 79% of HIVAN in AA could be prevented if European-derived or non-African derived *MYH9* variants were inherited. Sixty percent of AA in the general population possessed one *MYH9* risk allele compared to 4% of EA, and 35% of AA are homozygous for *MYH9* risk alleles compared to only 1% of EA. Ethnic differences in *MYH9* genotype distributions seem to account for the excess risk of non-diabetic ESRD observed in AA.^{51;52}

The realization that approximately 4-5% of AA individuals inheriting two copies of *MYH9* risk variants ultimately developed FSGS (personal communication, Dr. Jeffrey Kopp) demonstrated that additional factors or "second hits" must be involved in the initiation of *MYH9*-associated nephropathy. Since approximately 20% of AA *MYH9* risk homozygotes with HIV-1 infection develop HIVAN (personal communication, Dr. Jeffrey Kopp), a fourfold increase over rates seen in the absence of HIV infection, we postulate that HIV-1 is one environmental co-factor. Additional co-factors could include non-HIV-1 environmental exposures (gene-environment interactions) or could result from gene-gene interactions (particularly between *MYH9* and other podocyte-specific gene polymorphisms). The proposed

second hit model for initiation of HIVAN is not limited to this disease, but is also expected in the full spectrum of "MYH9-associated nephropathies" (FSGS and global glomerulosclerosis), since *MYH9* is thought to be an overarching "renal failure susceptibility gene" independent of HIV infection.

Murine models of HIVAN suggest the existence of podocyte-specific gene polymorphisms that, with *MYH9*, may produce gene-gene interactions. Linkage analysis of HIVAN in mice reveal susceptibility loci located on chromosomes 3 (*HIVAN1*) and 13 (*HIVAN2*).^{54,55} Expression quantitative trait locus (eQTL) analysis of podocyte genes in an HIV-1 transgenic mouse model is a potentially powerful tool for detecting HIVAN genetic susceptibility in the murine model, with further implications for human disease. Transcript levels of the podocyte gene nephrosis 2 homologue (*Nphs2*) were shown to be heritable and controlled by an ancestral cis-eQTL, inducing threefold variation in gene expression. Downstream changes in other podocyte genes were induced by *Nphs2* expression. *Nphs2* expression is further controlled by two trans-eQTLs localizing to nephropathy susceptibility loci (*HIVAN1* and *HIVAN2*). This report demonstrated that transcript levels of *Nphs2* and other podocyte-expressed genes are networked. The genetic response to HIV-1 infection (a gene-environment interaction) appeared to alter this network and produce HIVAN. This would appear relevant to the human disease, where the presence of *MYH9* risk alleles and HIV-1 infection do not universally initiate HIVAN.

Novel environmental factors potentially involved in *MYH9*-associated HIVAN

HIVAN illustrates that both host genetic factors and environmental exposures are jointly required for the initiation of kidney disease, with evidence of the role of *MYH9* genotype and of infection of renal cells by HIV-1. As stated above, we believe that factors other than HIV infection may be necessary for the initiation of HIVAN in *MYH9* homozygotes (Figure 1). It also remains possible that *MYH9*-induced abnormalities in platelet function contribute to glomerular injury.⁵⁶

As HIV is a lymphotropic virus and causes immunodeficiency, other lymphotropic viruses, such as human herpes virus (HHV)-6, cytomegalovirus (CMV), and human T-cell lymphotropic virus-I (HTLV-I) and HTLV-II have the potential to contribute to *MYH9*-associated FSGS, in the presence or absence of HIV-1 infection.^{57–59} After primary infection, HHVs maintain latent persistence, typically punctuated by sporadic episodes of symptomatic lytic activation. After kidney transplantation, renal biopsies often reveal positive polymerase chain reaction for CMV and HHV-6.⁶⁰ Immunosuppression facilitates reactivation of these viruses, and HIV-infected patients are at high risk. In addition, CMV and HTLV-I/II share transmission routes with HIV and are likely more prevalent among those with HIV infection. It is possible that exposure to non-HIV lymphotropic viruses could interact with *MYH9* genotype to initiate *MYH9*-nephropathy.

Viruses infecting the nephro-urinary system could also potentially act as second hits in the development of HIVAN, especially in patients with advanced immunodeficiency. BK and JC polyoma viruses infect the urologic system and are associated with nephropathy.⁶¹ It is thought that viremia during primary JC and BK polyomavirus infections results in seeding of the kidney, establishing clinically latent infection. Approximately 30–50% of normal individuals have detectable BK or JC virus sequences in renal tissue obtained at surgery or autopsy, and PCR has demonstrated BK and JC viruria in asymptomatic non-immunocompromised adults.⁶² BK nephropathy has been reported in transplanted and HIV-infected patients.^{61,63} These findings suggest that BK and JC polyomavirus could be infections (or co-infections with HIV) that might initiate *MYH9*-associated nephropathy. Further research is needed in order to assess the role of these or other novel HIVAN risk factors among genetically at-risk individuals. Table

2 lists viral infections that we postulate could initiate *MYH9*-associated nephropathy or HIVAN and provides data on the prevalence of positive serology, viremia, and viruria in immunocompetent subjects. No data on the prevalence of these viruses in HIV-infected patients are available.

Hepatitis C (HCV) and hepatitis B (HBV) virus share transmission routes with HIV and could potentially be involved in the pathogenesis *MYH9*-associated nephropathy. While epidemiological analyses show a link between HCV seropositivity and risk for ESRD,⁶⁴ a role for HCV in the pathogenesis of HIVAN is unknown. Likewise, HBV-co-infection (HBV surface antigen positivity) is reportedly present more often than in the general HIV population,³ but involvement in HIVAN has not been established.

Conclusions

HIVAN is a common cause of ESRD in AA. HIV-1 infects podocytes comprising the glomerular filtration barrier and causes FSGS. HIVAN is most often a complication of late stages of HIV infection, and HAART is partially protective. While polymorphisms in the *MYH9* gene are strongly associated with HIVAN in AA, not all HIV-infected patients who are at risk based upon their *MYH9* alleles develop HIVAN. Since the majority of HIV-infected *MYH9*-risk homozygotes do not develop nephropathy, additional environmental and/or inherited factors are clearly required. Based on the results of murine transgenic models of HIVAN, we postulate that *MYH9*-podocyte-specific gene interactions may increase susceptibility to human HIVAN. Also, based on the immune effects of HIV-1 we postulate that other lymphotropic and/or nephropathic viral infections (gene-environment interactions) may increase the risk for developing *MYH9*-associated HIVAN. Further research is urgently needed to detect these novel HIVAN risk factors and develop methods to block the development of HIVAN among genetically at-risk individuals. It is now clear that HIVAN lies within the broad spectrum of "*MYH9*-associated nephropathy," kidney diseases including idiopathic FSGS and global glomerulosclerosis in non-HIV-infected individuals.

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Figure 1.

Potential co-factors involved in *MYH9*-associated HIVAN. Abbreviations: HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy.

Incidence and prevalence of HIVAN among HIV-infected African Americans. Abbreviations: HIVAN, HIV-associated nephropathy; TDCCJI, Texas Department of Criminal Justice Inmates.

Table 1

Reference #	Location	Study Type	Definition of HIVAN	HIVAN Prevalence	HIVAN Incidence
15	Galveston, TX	Cross-sectional	Biopsy or clinical	3.5% (10/282)	
16	TDCCJI, Tx	Cross-sectional, Post-mortem	Autopsy	12% (25/209)	
2	Baltimore, MD	Longitudinal	Biopsy or clinical		10.1/1000 person-years
9	Baltimore, MD	Longitudinal	Biopsy or clinical		1% per year

Table 2

Viral infections potentially associated with *MYH9-associated* HIV-associated nephropathy. Abbreviations: HHV, human herpes virus; CMV, cytomegalovirus; HTLV, human T-cell lymphotropic virus; PCR, polymerase chain reaction.

Virus	% seroprevalence in U.S. population	% detectable blood PCR, non-immunocompromised	% detectable urine PCR, non-immunocompromised
HHV-6 A/B	60%–100	30% (type B)	---
CMV	37%–70	1%–43%	---
HTLV-I	2%–15	---	---
HTLV-II	2%–15	---	---
JC polyoma	60%–80	0.9%	38%–72%
BK polyoma	60%–80	8.2%	14%–43%