TABLE 226-6 HOST GENETIC FACTORS THAT INFLUENCE RISK OF HIV-1 ACQUISITION AND RATES OF HIV-1 DISEASE PROGRESSION (*CONTINUED*)

Gene[a]	Genetic Variation	Mechanisms[b]	Genetic Effect on HIV-AIDS[c]
PARD3B	rs11884476 (C→G), near exon 20	Direct interaction with HIV, signaling through SMAD family of proteins	rs11884476-G associated with slower progression to AIDS
Others			
ApoE	E4 allele	E4 enhances HIV cell entry in vitro	ApoE4/E4 associates with rapid AIDS onset and dementia
ApoL1/ MYH9	Several risk haplotypes including G1	Unknown	Increased risk for HIV-associated nephropathy
RYR3	ORF SNP (A →G), rs2229116	Unknown, potential impact on calcium signaling and homeostasis	rs2229116-G associated with subclinical atherosclerosis
PROX1	rs17762192-G, 36kb upstream of *PROX1*	Unknown, presumably due to its impact on PROX1 expression, which is a negative regulator of IFN-γ	rs17762192-G: reduced rate of disease progression
Gene–Gene Interaction			
KIR+HLA	KIR3DS1 + HLA-Bw4-80Ile	Altered NK cell activity required to eliminate HIV-infected cells	KIR3DS1 with HLA Bw4-80I +: delayed AIDS onset
	HLA-C1 + KIR2DL3,	Reduction of inhibitory KIR likely results in increased immune activation; impaired killing of latently infected cells; and a higher proviral burden	HLA-C1+/KIR2DL3+: better immune recovery after viral load suppression on ART
LILRB2+HLA	LILRB2 + HLA class I	Regulation of dendritic cells by LILRB2-HLA engagement	Control of HIV-1
CCL3L1+ CCR5	Low *CCL3L1* gene copies + detrimental *CCR5* genotypes	Low CCL3L1 and high CCR5 expression	Increased HIV/AIDS susceptibility and reduced immune reconstitution during ART

[a]Representative genes and polymorphisms and [b]possible mechanisms are listed. [c]Some of the associations are population specific and may display cohort-specific effects.

Note: Apobec, apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like; ApoE, apolipoprotein E; ART, antiretroviral therapy; CCL, CC ligand; CCL3L, CCL3-like; CCR5, CC chemokine receptor 5; CRP, C-reactive protein; CXCR6, chemokine (C-X-C motif) receptor 6; DARC, Duffy antigen receptor for chemokines; HCP5, HLA class I histocompatibility antigen protein P5; HHE, human haplogroup E; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; LILRB2, leukocyte immunoglobulin-like receptor B2; KIR, killer cell immunoglobulin-like receptors; KS, Kaposi's sarcoma; MBL, mannose-binding lectin; MHC, major histocompatibility complex; MICA: MHC class I polypeptide-related sequence A; ORF, open reading frame; PARD3B, par-3 family cell polarity regulator beta; PROX1, prospero homeobox 1; PSORS1C3, psoriasis susceptibility 1 candidate 3; SNP, single nucleotide polymorphism; rs#, SNP identification number in SNP database from NCBI; UTR, untranslated region; ZNRD1, zinc ribbon domain containing 1; +, present, –, absent.

Sources: Sunil K Ahuja, MD, Weijing He, MD, and Gabriel Catano, MD. Reviews for additional information: P An et al: Trends Genet 26:119, 2010; J Fellay: Antivir Ther 14:731, 2009; RA Kaslow et al: J Infect Dis 191:S68, 2005; D van Manen et al: Retrovirology 9:70, 2012; MP Martin et al: Immunol Rev 254:245, 2013; S Limou et al: Front Immunol 4:118, 2013.

These SNPs are within or in the vicinity of *HCP5*, *HLA-C*, *MICA*, and *PSORS1C3* genes. The protective effects of the SNPs in *HCP5* and *MICA* may relate to their linkage with known protective *HLA-B* alleles. The protective *HCP5* allele is in linkage disequilibrium with the HLA-B*57:01, and the protective *MICA* allele tags with the HLA-B*57:01 and B*27:05 alleles. The protective *HLA-C* SNP is associated with higher HLA-C expression, and this effect is thought to be due to the altered binding of a microRNA to the *HLA-C* mRNA. Higher HLA-C expression has been associated with beneficial HIV phenotypes. The mechanism associated with the SNP in *PSORS1C3* is unknown. GWAS in African Americans identified a SNP that tags the HLA-B*57:03 allele that is known to associate with lower virologic setpoint and slower disease course. Together these GWAS data underscore the importance of variations in HLA class I loci in control of viral replication.

GENETIC ASSOCIATIONS WITH SPECIFIC AIDS AND NON-AIDS CONDITIONS • Carotid artery disease Many of the non-AIDS events in HIV-infected individuals resemble those related to immune senescence and those found in the HIV-uninfected aging population. A functional SNP in the ryanodine receptor 3 (*RYR3*) gene was found to be associated with an increased risk of common carotid intima–media thickness (cIMT), which is a surrogate for subclinical atherosclerosis. Functional studies on RYR3 and its isoforms demonstrate a major role of these receptors in modulating endothelial function and atherogenesis via calcium signaling pathways, providing a biologically plausible mechanism by which the SNP in *RYR3* may associate with increased cIMT risk.

Renal disease HIV-1-associated nephropathy (HIVAN) is a form of focal sclerosing glomerulonephritis caused by direct infection of kidney epithelial cells with HIV. HIVAN is more common in persons of African descent. There is evidence that polymorphisms in the *MYH9* gene and in the neighboring *APOL1* gene are a strong determinant of susceptibility to HIVAN in African Americans. The effect of carrying two *APOL1* risk alleles explains nearly 35% of HIVAN. The mechanisms by which *MYH9*/*APOL1* variants predispose to HIVAN are currently unknown.

HIV-associated neurocognitive disorder HIV-associated neurocognitive disorder (HAND) comprises a spectrum of neurocognitive deficits due to HIV infection. Variations in the apolipoprotein E (ApoE) gene have strong associations with Alzheimer's disease in the HIV-uninfected population. In HIV-infected persons, possession of the *ApoE4* allele has been associated with several cognitive outcomes including dementia, peripheral neuropathy, and impairment in cognition and immediate and delayed verbal memory. Macrophage recruitment and activation plays a central role in the development of many of the HAND syndromes. Variations in chemokines that play an influential role in macrophage activation and recruitment, namely *CCL2* (MCP-1) and *CCL3* (MIP-1α), have been shown to alter the risk of developing HAND. Variations in mitochondrial genes also have been associated with risk of AIDS and HAND.

ASSOCIATIONS WITH ART-RELATED ADVERSE EVENTS Abacavir, an effective antiretroviral agent, is associated with significant risk of hypersensitivity reactions (2–9% of cases). Interestingly, while the *HLA-B*57:01* allele is associated with a slower HIV disease course, possession of this allele is associated with a higher risk of abacavir-associated hypersensitivity. Pharmacogenetic screening for the HLA-B*57:01 allele is recommended before initiation of abacavir treatment.

NEUROPATHOGENESIS IN HIV DISEASE

While there has been a remarkable decrease in the incidence in the severe forms of HIV encephalopathy among those with access to treatment in the era of effective cART, HIV-infected individuals can still experience milder forms of neurocognitive impairment despite adequate cART. A variety of factors may contribute to the neurocognitive decline, which includes lack of complete control of HIV replication in the brain, production of HIV proteins that may be neurotoxic, low CD4+ T cell nadir, chronic immune activation, comorbidities such as