

The Role of Host Genetics in the Susceptibility for HIV-associated Neurocognitive Disorders

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Abstract Despite progress in the treatment of the Human Immunodeficiency virus (HIV), there continues to be a high prevalence of infected individuals who develop neurocognitive deficits and disorders. Our understanding of the potential cause of HIV-associated neurocognitive disorders (HAND) continues to develop on many fronts. Among them is the study of host genetics. Here, we review the most current information regarding the association between host genetics and risk for HIV infection, AIDS, and HAND. We focus on the role of dopamine dysfunction in the etiology of HAND, and propose a number of genetic polymorphisms within genes related to dopaminergic functioning and other neurobiological factors that may confer vulnerability or protection against HAND.

Keywords HIV-associated neurocognitive disorders · Polymorphism · Dopamine · HIV-encephalitis · HIV-associated dementia

Abbreviations

HIV Human immunodeficiency virus
HAND HIV-associated neurocognitive disorders

AIDS Acquired immunodeficiency syndrome
HACMC HIV-1-associated cognitive/motor complex
MCMD HIV-1-associated minor cognitive/motor disorder
HAD HIV-associated dementia
CNS Central nervous system
CCR Chemokine receptor
MCP-1 Monocyte chemo attractant protein-1
HIVE HIV encephalitis
TNF Tumor necrosis factor
IL Interleukin
MRI Magnetic resonance imaging
fMRI Functional magnetic resonance imaging
MRS Magnetic resonance spectroscopy
PET Positron emission tomography
DA Dopamine
DAT1 Dopamine transporter
DRD Dopamine receptor
CSF Cerebrospinal fluid
HAART Highly active antiretroviral therapy
GP Genetic polymorphism
mRNA Messenger ribonucleic acid
SDF-1 Stromal cell-derived factor-1
RANTES Regulated upon Activation, Normal T-cell Expressed, and Secreted
COMT Catechol-*O*-methyltransferase
VNTR Variable nucleotide tandem repeat
ADHD Attention deficit/hyperactivity disorder
DBH Dopamine-beta-hydroxylase
BDNF Brain derived neurotrophic factor
ApoE Apolipoprotein E
DARPP-32 Dopamine and cAMP-regulated phosphoprotein of molecular weight 32 kDa
NNTC National NeuroAIDS Tissue Consortium
MACS Multicenter AIDS Cohort Study

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Soon after the first cases of Acquired Immunodeficiency Syndrome (AIDS) were identified in the late 1970s and early 1980s, it became clear that progressive cognitive impairment leading to dementia was a common consequence of the disease. The dementia syndrome associated with advanced infection by the Human Immunodeficiency Virus (HIV), characterized by subacute onset of cognitive impairment, behavioral changes, and progressive central motor abnormalities, was first systematically described and termed *AIDS Dementia Complex* by Navia and colleagues in 1986 (Navia et al. 1986). At the time, this condition was reported to be the initial AIDS-defining diagnosis for as many as 20% of infected individuals (Navia and Price 1987). Various terms have since been used to describe this syndrome, including *HIV dementia*, *AIDS-related dementia*, and *subacute encephalitis*. Terminology adopted by the American Academy of Neurology (AAN) in 1991 and World Health Organization (WHO) in 1990 is currently the most commonly used. *HIV-1-associated cognitive/motor complex* (HACMC) describes the cognitive and motor syndromes associated with AIDS, including *HIV-1-associated minor cognitive/motor disorder* (MCMD) and the more severe *HIV-1-associated dementia* (HAD). In addition to these clinical syndromes, still more individuals suffer from subsyndromal HIV-related cognitive deficits that appear insidiously and may cause minor impairments in the capacity to work and function (Bornstein et al. 1993). More recently updated criteria were proposed that capture the spectrum of neurocognitive deficits that are due to HIV, from asymptomatic neurocognitive deficits without deficits in day-to-day functioning to full blown dementia (Antinori et al. 2007). The term for this broad classification is *HIV-associated neurocognitive disorders*, or HAND, which we will use herein to describe the various forms of neurocognitive dysfunction due to HIV.

Over two decades of research have examining the natural history and neurobiological causes of HAND have led to many insights, yet many questions remain. HIV enters the central nervous system (CNS) soon after initial infection, during the initial period of systemic viremia (Palmer et al. 1994; Persidsky and Poluektova 2006; Resnick et al. 1985). The predominant mechanism of entry is via macrophages/monocytes (Gendelman et al. 1989). The virus then spreads and replicates within the brain, infecting microglia and additional macrophages, the primary sources of productive infection in the brain (Shapshak et al. 1992; Yoshioka et al. 1992). Infection of these monocytic/macrophage cells occurs when the viral envelope protein gp120 binds to a CD4 receptor on the cell surface in conjunction with one of a variety of chemokine receptors, primarily CCR5 but also CCR3 and CXCR4, or a combination thereof (Dragic et al. 1996; He et al. 1997). HIV finds a sanctuary within the brain (Clements et al. 2005), in part

because most current antiretroviral medications are unable to cross the blood–brain barrier in sufficient quantities to fully inhibit replication (Thomas 2004), and because long-lived infected cells such as CNS macrophages and microglia provide a reservoir for the virus (Kramer-Hammerle et al. 2005). There is also evidence that HIV is able to infect choroid plexus (Falangola et al. 1995), brain capillary endothelial cells and astrocytes (Wiley et al. 1986). Prior research indicates that HIV segregates into separate compartments within the central nervous system (CNS), where each can evolve independently (Petito 2004; Shapshak et al. 1999). In some cases, this may result in the development of viral strains that are adapted to the CNS, and/or the development antiretroviral drug-resistant strains (Smit et al. 2004).

A full inflammatory response, which might be capable of destroying the virus, is limited within the CNS (Galea et al. 2007), presumably because CNS cells have a limited capacity to regenerate. However, the brain's own defenses, including an influx of CD8+ cells, typically restrict productive HIV infection until a second wave of infected monocytes crosses the blood–brain barrier (Persidsky and Poluektova 2006). This second wave typically occurs in advanced disease and may be triggered by advanced immuno-suppression outside the CNS, as marked by a decline in CD4+ cells and breakdown in the ability of the immune system to control viral replication, or by an increase in chemo-attractant substances and adhesion factors in the brain (Maslin et al. 2005). In vitro, the migration of monocytes through a model of the blood–brain barrier is increased via the secretion of chemokines (Persidsky et al. 1997, 2000), such as monocyte chemo attractant protein-1 (MCP-1) (El-Hage et al. 2006; Maslin et al. 2005). Elevated levels of monocyte chemo attractant protein-1 (MCP-1) are also associated with subcortical brain damage in vivo, as measured by diffusion tensor imaging techniques applied to the human brain (Ragin et al. 2006). The infiltration of infected monocytes could lead to the further seeding of the virus in the CNS and the triggering of neurotoxic processes that lead to inflammation, progressive neurodegeneration, and eventually HAND (Gartner 2000). The breakdown of the blood–brain barrier, which further opens the brain to the virus, may also be one of the crucial processes in the development of HAND (Avison et al. 2004a, b).

One of the key features of HIV encephalitis (HIVE), a condition thought to underlie most instances of HAND (Cherner et al. 2002), is neuronal loss (Mattson et al. 2005). However, the mechanisms by which neurons become damaged or neuronal loss occurs is not fully understood. Most investigators agree that productive infection of neurons and oligodendroglia does not occur, and that cytolytic viral infection does not result in either

neuronal loss or myelin damage in HIV. Rather, these processes result from at least two sources. The first is the direct effects of neurotoxic viral proteins such as gp120, gp41, nef, and tat, which are secreted by productively infected host cells (Persidsky and Poluektova 2006). Some of these proteins enable the virions to bind to chemokine receptors on neurons, likely setting off a chain of events within the neurons that ultimately leads to cell dysfunction and/or death. The second mechanism for neuronal and glial damage is mediated through the body's own immune response, in which infected or immunologically activated macrophages and microglia secrete neurotoxins or induce other neural cells to produce neurotoxins, such as tumor necrosis factor-alpha (TNF-alpha), interleukin 1 (IL-1), and quinolinic acid (Anderson et al. 2002; Brabers and Nottet 2006). Ultimately, significant neuronal dysfunction and death is believed to result in the neurocognitive and neurological deficits that characterize HAND (Persidsky and Gendelman 2003). Based on a wealth of research described in detail below, variation in genes that involved in the body's immune response are predictive for risk of infection and for disease progression.

Neuroimaging and neuropathological studies have delineated the structural and functional correlates of HAND. Research suggests that HIV-related neuropathology is particularly prevalent in subcortical structures, especially the *putamen* and *caudate* nuclei of the basal ganglia (Berger and Nath 1997; Dal Pan et al. 1992), the *substantia nigra* (Itoh et al. 2000), and the white matter tracts connecting subcortical nuclei with the frontal lobes (Power et al. 1993). Clinical studies have also shown HIV to have particular adverse impact upon dopaminergic (DA) neurons and/or systems, and there is some evidence to connect this impact to specific cognitive, motor, and behavioral deficits in affected persons. Indeed, since the early days of the epidemic, investigators have reported Parkinsonian signs and symptoms, including hypersensitivity to DA-blocking drugs, apathy, and motor slowing/incoordination in AIDS (Arendt and von Giesen 2002; Edelman and Knight 1987; Kiebertz et al. 1991; Koutsilieris et al. 2002; Navia et al. 1986). Structural MRI studies of individuals with HAND have found reduced basal ganglia volume (Aylward et al. 1993) and evidence for increased blood–brain barrier permeability in this region (Berger et al. 2000), findings supported by a recent MRS study (Avison et al. 2004a, b). Functional imaging studies have revealed that hypermetabolism of the basal ganglia is a hallmark feature of HAND during the early stages of infection, and this continues to increase over time until the late stages of dementia, suggesting an increase of activity within this nucleus to compensate for neuronal dysfunction or loss (Hinkin et al. 1995; Rottenberg et al. 1996; van Gorp et al. 1992). Recently, Wang and colleagues (Wang et al. 2004), using positron emission tomography (PET),

found evidence that a decrease in pre-synaptic dopamine transporter (DAT1) may be a significant contributor to the pathogenesis of HAND.

The role of DA in the pathogenesis of HAND is further bolstered by in vitro and animal studies. The HIV proteins tat and gp120 demonstrate neurotoxicity in selective neuronal populations, and DA neurons appear to be particularly vulnerable (Jones et al. 1998; Nath and Geiger 1998). Further, gp120 has been shown to block DA uptake in neurons, resulting diminished cellular function (Bennett et al. 1995). Animal studies have shown loss of striatal neurons and diminished levels of DA following injection of tat into the lateral ventricle and striatum (Jones et al. 1998; Nath et al. 2000). In humans, homovanillic acid, a marker of CNS DA levels, has been shown to be reduced in brain tissue and CSF of those with AIDS, and more so in those with evidence of neurobehavioral impairment (Berger et al. 1994; Engelmayer et al. 2001; Larsson et al. 1991; Sardar et al. 1996). Finally, the heaviest concentrations of HIV are found in the basal ganglia and frontal lobes, further implicating the fronto-striatal system as particularly vulnerable to infection (Wiley and Nelson 1990). When correlated to the clinical observations of Parkinsonism, reduced striatal volume, and increased HIV viral load in the subcortical regions, it is possible to postulate that one of the causes of HAND is a neurotoxic effect of HIV on dopaminergic neurons within the fronto-striatal system. It further opens the discussion of whether known genetic variations in the DA functioning might exacerbate or protect an individual from developing HAND.

To summarize, the neurobiological and neuroanatomical correlates of HAND are areas of current concern and appear to involve a variety of factors, including host immune response and breakdown of the blood–brain barrier that lead to dysfunction primarily of the DA neurons within the fronto-striatal system.

Prevalence and Predictors of HAND in the HAART Era

The widespread use of highly active antiretroviral therapy, or HAART, has resulted in another interesting observation; despite substantial improvements in life expectancy and lowered incidence of HAND, the syndrome, and more commonly subsyndromal neuropsychological deficits, continue to occur at a high prevalence rate (Ances and Ellis 2007; Dore et al. 2003; Valcour et al. 2004; Wojna et al. 2006), although not all studies have found evidence of this (Cysique et al. 2004). Rates of HIV observed at autopsy are also on the rise (Langford et al. 2003; Neuenburg et al. 2002), although this too has not been uniformly observed (Gray et al. 2003), and in fact some investigators propose that the characteristics of HIV have changed since the

inception of antiretroviral therapy (Bell 2004). Thus, as indicated by many studies, even relatively healthy HIV+ individuals may be at risk for HAND, and HAART does not appear to be adequately protective (D'Hooge et al. 1999). Consequently, searching for means of predicting who is most vulnerable for developing these syndromes, or identifying early indicators, has become a critical area of NeuroAIDS research. As in the past, immuno-suppression, reflected in virologic factors such as CD4+ T-cell counts, is the best predictor of risk for HAND. However, the mean level of such measures has changed in the HAART era such that deficits are presenting in those with higher CD+ counts than in the past (Dore et al. 2003). Other risk factors that can be identified before immunologic suppression are now being considered with greater credence. With such information, clinicians would be better equipped to initiate advanced prophylactic strategies and other preventative measures, and researchers would have a greater degree of control in considering confounding factors when designing studies.

Currently, there exist a number of factors which are useful for identifying individuals who are inherently or chronically at risk for HAND. These include demographic characteristics, medical co-morbidities, and lifestyle behaviors. Ethnicity, for example, may be associated with risk of developing HAND. Data from the National Neurological AIDS Bank cohort, a multi-ethnic sample from the greater Los Angeles area, suggests that African Americans are at greater risk for developing HAND, even when virologic, drug use, and educational factors are considered (Levine et al. unpublished data). Age, too, has come to the fore as an important risk factor for HAND (Becker et al. 2004; Cherner et al. 2004; Valcour et al. 2004), and there are a number of ongoing studies that continue to characterize the neurobehavioral characteristics of this growing population. Comorbid medical and psychiatric conditions also confer greater risk for neuropsychological deficits and HAND. For example, hepatitis C co-infection is now accepted as a significant risk factor for development of HAND (Cherner et al. 2005; Tozzi et al. 2005). Diabetes (Valcour et al. 2005) and anemia (Qureshi et al. 1998) have also been found to be more prevalent in those with HAD. Lifestyle behaviors, in particular alcohol and drug use, also appear to confer risk for HAND. For example, stimulant use is believed to have a synergistic relationship with HIV in creating neuropathological and adverse behavioral changes (Levine et al. 2006; Rippeth et al. 2004). A proposed mechanism for this synergistic impact is that both HIV and stimulants are particularly harmful to DA neurons in the fronto-striatal system. Long-term use of methamphetamine and cocaine has been shown to have an adverse impact on DA functioning and related neuroanatomical regions (Ernst et al. 2000; Jacobsen et al. 2001; Little et al. 1999; Volkow

et al. 2001), and this may be especially true in those with HIV (Nath et al. 2001).

The pressing need to identify additional risk factors for HAND has brought attention to the role of host-genetics in relation to HIV-susceptibility and disease progression. Variations of amino acid sequences within genes that result in alterations in the functioning of their product, called functional genetic polymorphisms (GPs), have been a useful tool in determining the physiological processes that lead to HAND. GPs are essentially mutations that are relatively common, occurring at a rate of $\geq 1\%$ in the population (Plomin et al. 2001). GPs commonly consist of the substitution of one nucleotide by another, called a single nucleotide polymorphism (SNP). Some GPs consist of single-base mutations resulting in the insertion or deletion of a nucleotide, which in turn results in a frame shift during transcription. This can lead to significant alteration of the resulting protein and have serious effects upon physiological functions and behavior. GPs may also consist of repeated sequences of amino acids called variable nucleotide tandem repeats (VNTR) which can result in adverse consequences, as in the case of Huntington's disease. There can be many GPs within a single gene, although most are non-functional. That is, they do not alter the activity of the gene product or replication process. The identification of GPs has been a useful tool in studying some of the host physiological processes that lead to HAND. To date, only a few have been identified, and these are generally found in genes that produce chemokines, chemokine receptors, and other cytokines. However, it seems highly plausible that GPs previously implicated in other neurologic and psychiatric conditions, especially those related to DA functioning, may play a significant role in vulnerability for HAND. In the remainder of this paper, we discuss the current state of research regarding the former GPs, and propose additional direction for the inclusion of the latter.

Polymorphisms of Chemokines and Chemokine Receptors

Chemo-attractant cytokines, or chemokines, and their receptors play a number of roles within the central nervous system, including regulation of leukocyte trafficking, modulation of cell adhesion, cytokine secretion, cell activation, apoptosis, angiogenesis, viral pathogenesis, and modulation of synaptic transmission, among others (Cartier et al. 2005). Chemokines are classified into four classes: CC, CXC, XC, and CX3C. They can also be classified based on their primary function: inflammatory versus homeostatic. Under normal (i.e., non-pathological) conditions, only select chemokines and chemokine receptors are

expressed in specific areas within the CNS; however, pathological states, such as HIV infection, result in widespread and varied chemokine expression.

As discussed above, macrophages and lymphocytes become infected when the HIV-viral envelope protein gp120 binds to a chemokine receptor in conjunction with the CD4 receptor. The various types of chemokine receptors appear to be associated with different strains of HIV-1. For example, macrophage-tropic, or M-tropic HIV-1 viruses use the CCR5 receptor, whereas T-tropic (infecting T-cells) strains use the CXCR4 receptor to enter the cells. Researchers have examined the expression of the CXCR4, CCR2, CCR3, and CCR5 receptors in the brains of those with HIV. These receptors appear to be up-regulated in the presence of the virus. While beyond the scope of this review, the anatomical distribution of these receptors is varied, as is the cell types on which they are expressed.

Various GPs of chemokine receptors have been found to affect an individual's susceptibility for HIV infection, disease progression, and risk for HAND. In the early course of infection, CCR5 is the most common chemokine receptor utilized by the virus to enter cells. Numerous GPs in the gene that produces CCR5 have been reported. The first was CCR5-delta-32, the result of a large deletion of nucleotides. Early studies demonstrated that homozygosity (i.e., having the same version of the gene, or allele, from each parent) for this allele conferred high resistance to HIV infection (Liu et al. 1999; Samson et al. 1996). However, heterozygosity (i.e., having only one of this allele) was not found to confer resistance to infection, although numerous studies have associated it with slower disease progression. For example, Boven and colleagues (Boven et al. 1999) found that not a single case among their sample of European American individuals with HAD had a CCR5-delta-32 allele, which normally occurs in 10–20% of individuals with northern European ancestry. Of note, those individuals who were homozygous for the wild-type (i.e., non-polymorphic) CCR5 allele had significantly greater viral mRNA expression within their macrophages, further bolstering evidence for the CCR5-delta-32 allele's protective quality. Others have confirmed the reduced occurrence of CCR5-delta-32 in those with HAD (van Rij et al. 1999). Meyer and colleagues (Meyer et al. 1997) also found that heterozygosity for the CCR5-delta-32 allele was associated with slowed disease progression, primarily during the earlier years of HIV infection. Further, those with this genotype were less vulnerable to pneumocystis carinii pneumonia and toxoplasmosis, common AIDS-defining opportunistic infections. More recently, Singh and colleagues (Singh et al. 2003) found that children heterozygous for the CCR5-delta-32 allele had slower disease progression and less cognitive impairment than those homozygous for the wild-type. However, this CCR5-delta-32 allele was uncommon

in their sample of mostly African American children. Interestingly, the authors reported that among those homozygous for the CCR5 wild-type allele, another common CCR5 GP termed 59029-A/A was associated with more rapid disease progression. Note that the frequency of the CCR5-delta-32 allele varies significantly across ethnic groups, appearing much more frequently in European Americans than in African Americans. Such differences in the frequencies of these alleles among ethnicities warrants further investigation, as these factors may differentially affect rates of progression towards HAND.

The minor HIV-1 co-receptor CCR2 has also been examined in its relationship to disease progression. Smith and colleagues found that a common SNP, the CCR2-V64I, was associated with slower disease progression in adults (Smith et al. 1997). In fact, those that were heterozygous for this allele developed AIDS 2–4 years later than those who were homozygous for the CCR2 wild-type allele. While this finding was not replicated in a later study that used a cohort of children (Singh et al. 2003), a still later study found CCR2-V64I to be associated with slower progression towards neurocognitive impairment in adults (Singh et al. 2004).

The CXCR4 is a chemokine receptor that is generally exploited by the virus later in the course of infection, in about 50% of infected individuals (Michael and Moore 1999). In several in vitro studies, CXCR4 chemokine receptor activation by gp120 was implicated in HIV-associated neuronal damage (Hesseltger et al. 1998; Kaul and Lipton 1999; Meucci et al. 1998). Although no functional GPs have been associated with CXCR4, GPs within the gene of its ligand, stromal cell-derived factor-1 (SDF-1), have been implicated in disease progression. Chemokine ligands compete with HIV for their corresponding receptors, and are thus believed to inhibit infection. SDF-1 is especially important during development and for neuronal functioning. After infection, SDF-1 has been noted to inhibit HIV-1 transmission by competing for CXCR4 binding due to its high expression in genital and rectal epithelium (Agace et al. 2000). Further, SDF-1 down-regulates the expression of CXCR4, thereby hindering infection by T-tropic HIV-1 strains. However, messenger-RNA levels of SDF-1 are elevated in HIV when compared to uninfected controls (Asensio and Campbell 1999; Zheng et al. 1999), suggesting that once infected, this chemokine is involved in the pathogenesis of HAND. Indeed, in vitro studies have shown SDF-1 to be toxic to neurons (Kaul and Lipton 1999; Kaul et al. 2005; Zheng et al. 1999). It was also recently reported that SDF-1 expression is dependent on interleukin-1-beta (Peng et al. 2006), another cytokine implicated in disease progression. To date, one SNP in the gene that produces SDF-1 has been found to play a significant role in AIDS and HAD. Winkler

and colleagues (Winkler et al. 1998) identified this widely common GP, SDF1-3'-A, which was shown to delay onset of AIDS in individuals homozygous for the allele. This protective effect of the GP was even more pronounced in individuals with longer durations of HIV infection. SDF1-3'-A was also recently reported to be more common in a cohort of HIV+ individuals who responded well to HAART compared to those whose viral loads remained elevated after one year (Puissant et al. 2006). However, others have found contrasting results. For example, Singh and colleagues (Singh et al. 2003) found that among their sample of primarily African American children, homozygosity for SDF1-3'-A was associated with more rapid progression and faster decline in neurocognitive ability, although they noted that this genotype was very rare in their sample. It may be that chemokines such as SDF-1 play different roles throughout development, explaining the sometimes contradictory results between studies using adults and those using children.

Monocyte chemo-attractant protein 1 (MCP-1), also called CCL2, is a chemokine that recruits monocytes and other immune cells to the site of tissue injury and infection, and is therefore believed to be responsible in part for the inflammatory response to HIV. MCP-1 is a ligand for CCR2 that is found on astrocytes, and it is elevated in the CNS of those with HAD. HIV infection results in elevated transcription of MCP-1 in astrocytes, via the viral protein Tat (Abraham et al. 2005). A GP in the MCP-1 gene has been found to have both protective and injurious effects. Gonzalez and colleagues (Gonzalez et al. 2002) found that homozygosity for the MCP-1-2578G allele was associated with 50% reduction in risk for HIV-1 infection. However, once infected, the same genotype was associated with accelerated disease progression and a 4.5-fold increased risk of HAD, possibly due to its pro-inflammatory nature and because it up-regulates HIV replication. Rovin and colleagues (Rovin et al. 1999) examined two GPs within regulatory region of the MCP-1 gene, hypothesizing that the level of the chemokine's expression dictates the degree of tissue leukocyte infiltration. They found that one SNP, in which guanine (G) was substituted for adenine (A), affected MCP-1 production. Specifically, monocytes from those in with the G allele had greater MCP-1 production after exposure to IL-1beta when compared to monocytes from individuals homozygous for the A alleles. The effects were dose dependent, so those that are homozygous for the G allele had even higher production. Thus, those with G alleles have more intense inflammatory reactions, which in turn may lead to neuronal damage and cognitive impairment.

Finally, it is worth noting that a variety of CCR5 ligands, including MIP-1-alpha, MIP-1-beta, and RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted), appear to inhibit transmission of the virus

(Cocchi et al. 1995), and that certain variants in the genes for these chemokines are associated with poorer prognosis. It has been reported that among European Americans, individuals who were homozygous for a particular haplotype (i.e., combination of SNPs that tend to be transmitted together from a parent) within the MIP-1-alpha gene developed AIDS at an accelerated rate (Gonzalez et al. 2001). Interestingly, this haplotype was not associated with disease progression among African Americans. Also among European Americans, those that were homozygous for a certain haplotype within the RANTES gene had a faster disease progression to AIDS and death, and those that lacked this haplotype were at a lower risk for becoming infected. Other SNPs within the RANTES gene have been associated with elevations in RANTES transcription and slower progressions to AIDS (Liu et al. 1999; McDermott et al. 2000).

Polymorphisms of Other Cytokines

A variety of other cytokines have been examined in their relation to HIV-related disease progression. Among these are the interleukins (IL), cytokines involved in immune system functioning and produced by a wide variety of cells. IL-2 has been shown to up-regulate the expression of CCR5 *in vivo*, thus making more available for use as HIV-co-receptors (Weissman et al. 2000). A SNP on the IL-2 gene, when associated with certain haplotypes, has been reported to reduce vulnerability for HIV infection (Shrestha et al. 2006). Do and colleagues examined the frequencies of a large number of IL-1 SNPs and haplotypes among individuals classified as either slow or rapid progressors, as well as a control group (Do et al. 2006). Only one SNP, occurring within an intron (i.e., non-coding region) in the IL-1Ra gene, was found to differ significantly between the groups. Others have also identified SNPs within the IL-1-alpha gene associated with HIV-1 replication in patients taking HAART (Price et al. 2004).

Tumor Necrosis Factor (TNF) is a pro-inflammatory cytokine that is involved in apoptosis, cellular proliferation and differentiation, viral replication, and in the regulation of immune cells. TNF-alpha is mainly produced by macrophages, but can also be synthesized by a broad variety of other cell types including lymphoid cells, endothelial cells, and even neuronal tissue. For example, microglia can release TNF-alpha and IL-1-beta, another pro-inflammatory cytokine, both leading to neuronal apoptosis via release of L-cysteine (Wesselingh et al. 1997; Yeh et al. 2000). Elevated TNF-alpha has many adverse effects upon the brain, including the potentiation of glutamate neurotoxicity (Chao and Hu 1994), disruption of ionic transport in astrocytes (Benos et al. 1994), damaging of

oligodendrocytes (Selmaj and Raine 1988) and cortical neurons (Gelbard et al. 1994), and increasing the permeability of the blood–brain barrier (Brabers and Nottet 2006). TNF-alpha levels may also be increased in infected individuals in response to viral proteins. Quasney and colleagues reported one SNP within the promoter region of the TNF-alpha gene that was associated with response to viral proteins. Possession of even one allele of this GP was associated with HAD, as compared to HIV+ individuals without dementia and a healthy control population (Quasney et al. 2001).

Polymorphisms of Neurophysiological and Neurotransmitter Factors

As described in a previous section, there is compelling evidence to suggest that dysfunction of DA-modulated neurons within the fronto-striatal system of the brain is the basis for many of the neurobehavioral deficits seen in those with HAND. However, neuropathological changes do not consistently correlate with clinical impairment, as some individuals are more vulnerable to developing neurocognitive disorders and deficits than others. One possible area that remains to be examined is the contribution of GPs that affect the metabolism and activity of DA. GPs within certain genes are associated with individual differences in DA functioning that may have observable neurophysiological and neurocognitive correlates, as well as differing degrees of risk for a variety of neuropsychiatric illnesses. While the effects of these GPs upon risk for psychiatric symptoms and performance on neuropsychological measures has been small, it is conceivable that in vulnerable individuals whose DA functioning is already compromised, such as those with HIV, the effects will be augmented. Thus, investigation of these DA-related GPs will be an interesting and perhaps fruitful area to explore in the NeuroAIDS context.

Catechol-*O*-Methyl-transferase (COMT)

One GP of particular interest to those studying neuropsychiatric illness lies within the COMT gene. COMT is most crucial for its role in DA catabolism within the prefrontal cortex, an area crucial for a variety of cognitive abilities. The COMT gene contains a highly functional and relatively common SNP resulting in methionine (met) being substituted for valine (val) during translation. This SNP results in altered enzymatic activity of COMT (Lachman et al. 1996), and subsequently greater availability of DA within the prefrontal cortex of those with the met allele. Homozygosity for the val allele has been linked to poorer

cognitive functioning in persons with schizophrenia (Bilder et al. 2002; Egan et al. 2001; Nolan et al. 2004), their relatives (Rosa et al. 2004), and healthy individuals (Malhotra et al. 2002). Further, functional neuroimaging studies have shown that individuals with the met allele do better on neuropsychological tests of executive functioning and working memory, which presumably assess prefrontal cortical function (Egan et al. 2001; Goldberg et al. 2003; Mattay et al. 2003). Such findings are particularly relevant to HIV, as a recent neuroimaging study suggested reduced neural processing capacity in working memory networks in those with HIV (Tomasi et al. 2006).

Dopamine Transporter Gene (DAT1)

DAT1 acts by aiding the re-uptake of synaptic DA into the pre-synaptic terminal. It is present in the striatum and ventral tegmentum, subcortical regions that are key sites in the pathogenesis of HAND. Reduced DAT1 may play a key role in the pathogenesis of HAD, as evidenced in the recent PET study described in a previous section (Wang et al. 2004). The polymorphism most commonly studied is a VNTR, in which a 40-base long sequence of nucleotides is repeated in the gene (Vandenberg et al. 1992). Alleles contain between 3 and 11-repeat copies of this VNTR. However, the 9-repeat and 10-repeat alleles are by far the most common forms of this polymorphism, and individuals homozygous for the latter have lower DAT1 availability and binding than those who have one or two alleles of the former. The presence of DAT1 in the striatum and ventral tegmentum also suggest a role in the neuropathology of HIV. Direct physiological correlates of this polymorphism have been shown in human neuroimaging studies. For example, it was recently demonstrated that individuals with the 10-repeat allele have metabolic findings consistent with more focused activation of working memory networks that include the prefrontal cortex (Bertolino et al. 2006). The authors also found that, in those individuals homozygous for both the COMT met allele and DAT1 10-repeat, an additive affect on brain activity was present during a working memory task. Thus, these GPs of interest may result in additive affects on DA functioning.

Dopamine Receptor Genes (DRD)

DRD genes, such as DRD4, have been of interest due to their regulation of DA's effects upon neurotransmission and neuromodulation. Perhaps the most studied DRD4 polymorphism is a VNTR on chromosome 11. The most common short form (i.e., less than 6 repeats) contains 4 repeats, while the most common long form contains 7

repeats (Benjamin et al. 1996). Homozygosity or heterozygosity for the long common form of the VNTR is associated with decreased responsiveness to DA agonists, possibly due to altered ligand binding or signal transduction (Lichter et al. 1993). Behaviorally, the long forms may be associated with deficits in attention, as seen in Attention Deficit/Hyperactivity Disorder (ADHD) (Smalley et al. 1998). In addition, a VNTR in the 5' regulatory region of the DRD4 has been found to be strongly associated with ADHD (Mill et al. 2003), methamphetamine abuse (Li et al. 2004), and novelty seeking behavior (Rogers et al. 2004). While there are no studies relating this to HIV or HAND, it is conceivable that persons who are more impulsive, more novelty-seeking, less attentive, and use more methamphetamine are at higher risk of both HIV infection and HAND.

A SNP in the DRD2 gene has also been reported to increase striatal DRD2 availability in humans (Hirvonen et al. 2004). Individuals who are homozygous for the C (cytosine) allele, who have the highest degree of striatal binding potential as a result, demonstrated poorer performance in a word serial position test (Xu et al. 2007). Further, as with DAT1, there is an additive effect with COMT on task performance.

Dopamine- β -Hydroxylase (DBH)

DBH is an enzyme that catalyzes the conversion of dopamine to norepinephrine. A functional GP exists within the DBH gene. Zabetian and colleagues found that this GP accounts for 35–52% of the variation in plasma-DBH activity among individuals from various ethnic groups, including African-Americans, European Americans, and Japanese (Zabetian et al. 2001). In addition, a VNTR within this gene has been associated with biochemical variability in the catecholamine pathway (Wei et al. 1997) and ADHD (Daly et al. 1999; Roman et al. 2002). Because functional polymorphisms such as these are likely to play a significant role in catecholamine activity, and subsequently behavior, their potential relationship to HAND should be examined.

Brain Derived Neurotrophic Factor (BDNF)

Brain derived neurotrophic factor (BDNF) is a neurotrophin that promotes neuronal survival and regulates the production and differentiation of neurons. BDNF plays a regulatory role in the DA and serotonin systems (Guillin et al. 2001; Mossner et al. 2000). Relevant to HIV, both in vitro and in vivo evidence suggests that BDNF may reduce the neurotoxic effects of gp120 in those with HIV (Nosheny et al. 2005).

A SNP has been identified resulting in a valine-to-methionine substitution during translation. This allele, termed Val66Met, appears to result in neurobehavioral alterations. Functionally, in vitro studies indicate that transfection with the met allele variant results in aberrant intracellular trafficking and secretion of BDNF protein compared to the val allele (Egan et al. 2003). In the same study, the authors showed an association between the met allele and diminished episodic memory in human subjects, with associated abnormal activation and decreased levels of n-acetyl aspartate (a marker of neuronal functioning) in the hippocampus as determined via brain MRS. The involvement of BDNF in memory-related activity was further supported by a fMRI study (Hariri et al. 2003), which showed that the met allele was associated with diminished hippocampal activity during encoding and retrieval processes. Furthermore, met allele carriers have been shown to have significant decreases in hippocampal and prefrontal cortex volumes (Pezawas et al. 2004). Finally, the Val66Met polymorphism is believed to be a modifying genetic factor in the expression of numerous neurologic and psychiatric conditions and symptoms, including psychosis, bipolar disorder, and ADHD (Zhang et al. 2006).

Apolipoprotein E (ApoE)

ApoE has long been implicated in the pathogenesis of Alzheimer's disease. However, more recently ApoE has become of interest in the pathogenesis of HAND (Corder et al. 1998; Diaz-Arrastia et al. 2004; Valcour et al. 2004). ApoE comes in three major isoforms; apoE2, -E3, and -E4, which are coded for by three alleles (epsilon 2, 3, and 4). E3 is the most common allele, while E4 has been found to confer risk of Alzheimer's disease. Recently, Valcour and colleagues (Valcour et al. 2004) showed that possession of the Apo4 allele conferred a greater risk for HAD in individuals over the age of 50. An earlier study also showed an increased frequency of HAD among E4 carriers (Corder et al. 1998). However, others have not found this association. Probing neuropathological correlates of ApoE, Diaz-Arrastia and colleagues (Diaz-Arrastia et al. 2004) examined host genetic polymorphisms and susceptibility for HIVE and vacuolar myelopathy. Drawing DNA from the brains and spinal cords of 270 patients who had died between 1989 and 1996, the authors did not find a consistent association between ApoE4 and pathologic findings of HIVE. However, the authors noted their small sample, and therefore lack of sufficient power, as a possible reason for null findings. In addition, while HIVE is thought to be a common pathological substrate for HAD, the two can occur independently of one another (Goplen et al. 2001).

Dopamine and cAMP-regulated Phosphoprotein of Molecular Weight 32 kDa (DARPP-32)

DARPP-32 is primarily found in regions receiving projections for DA neurons and is believed to integrate incoming information. It is most abundant in the neostriatum (Ouimet et al. 1992). A recent study by Meyer-Lindenberg and colleagues (Meyer-Lindenberg et al. 2007) demonstrated the key role DARPP-32 plays in the frontostriatal system. The authors described the cognitive, volumetric, and functional imaging correlates of common haplotypes consisting of 7 SNPs. The most common haplotype, present in 76% of their European-American sample, was found to be associated with enhanced performance on neuropsychological measures of executive functioning among schizophrenic patients and their unaffected relatives. The same haplotype was found to be associated with decreased neostriatal volume and activation during working memory tasks, interpreted by the authors as indicating more efficient processing. The overlap of these regions with those affected in HAND, and the cognitive functions implicated in the Meyer-Lindenberg study, make DARPP-32 a strong candidate for examination in the neuropathogenesis of HAND.

Conclusions

The identification of a variety of GPs that may play a role in the pathogenesis and deficits associated with HAND is an important and exciting aspect of NeuroAIDS research. This has almost exclusively involved genes associated with inflammatory processes, such as those coding for chemokine receptors and cytokines. The investigation of genetic factors involved in DA functioning, which may also be extended to other neurotransmitters and neurobiological factors, holds additional promise for understanding the neurophysiological basis of cognitive and psychiatric symptoms in this population, as well as for discovering novel pharmaceutical interventions for those at risk and for those who suffer from such symptoms. While it is acknowledged that the observable effect of individual GPs on behavior may be subtle, studies examining gene–environment interactions in the etiology of psychiatric disorders suggest that such effects may be amplified in those in which an environmental stressor (e.g., HIV) is present (Thapar et al. 2007).

Because the phenotypes to be examined (e.g., memory, processing speed, depression) may be difficult to operationalize, inconsistent across studies, and problematic to quantify, large and relatively homogenous samples are required. Fortunately, there are currently a number of large studies monitoring, among other things, the natural evolution of HIV and its related disorders. Among these is the

National NeuroAIDS Tissue Consortium (NNTC), a group of brain banks that was established in 1998 to collect, store, and distribute specimens of nervous tissue, cerebrospinal fluid, blood, and other tissue from HIV+ individuals for scientific research. The NNTC consists of four sites and has neurobehavioral, virologic, genetic and medical data on over 1,800 HIV+ individuals, as well as brain tissue for a significant proportion of cases. The data are available to qualified researchers. An additional well-characterized cohort with available behavioral and genetic data is the Multicenter AIDS Cohort Study, which has been following HIV+ individuals and HIV– controls for over two decades.

Another consideration is the potential value of genome-wide-association (GWA) studies. While association studies examining candidate GPs continue to lead to further elucidation of the causes and correlates of disease, the vastness of the human genome strongly suggests that many GPs will be associated with vulnerability for HAND. Indeed, a recent GWA study identified SNPs associated with both HIV-related phenotypes (Fellay et al. 2007). Drawing from a collective sample from nine European cohorts (30,000+ participants), the authors chose 486 Caucasian individuals who met the strict criteria for their phenotypes of interest. Specifically, they examined the association between genotype and two phenotypes: (1) viral set point, defined as the average level of circulating virus during the non-symptomatic (pre-AIDS) phase, and (2) a “progression phenotype”, which was the time to treatment initiation or the time to the predicted or observed drop in CD4 cells below 350. Of the more than 555,000 SNPs genotyped, one located within the HLA complex P5 gene and another in the HLA-C gene explained 9.6% and 6.5% of total variation in HIV-1 set point, respectively. A third group of SNPs, located in or near the ring finger protein 39 gene and zinc ribbon domain containing 1 genes, explained 5.8% of the variation in disease progression. Such findings, as stated by the study authors, may lead to novel pharmaceutical therapies for those with HIV. Indeed, ever-evolving technology that currently allows genotyping of hundreds of thousands of SNPs in a single experiment may someday allow the characterization of all variation within the genome (Freimer and Sabatti 2007). Alternatively, exploiting the data available to the public through resources such as the International HapMap Project (<http://www.hapmap.org>) allows for the economical selection of SNPs covering extensive stretches of chromosomes for genome-wide-association studies.

The theories of brain and cognitive reserve (Satz et al. 1993; Stern 2002), based on the observation that some individuals are more resilient than others in the event of brain injury and neurodegeneration, are relevant to HAND. These theories, which suggest a compensatory or preservation

effect for such factors as education and brain size, may also be explained in part by genetic variation that can be captured in genetic association studies. For example, evidence from recent neuroimaging studies suggest reduced neural processing efficiency during cognitive tasks in those with HIV as compared to seronegative individuals (Chang et al. 2004; Tomasi et al. 2006). Therefore, genes involved in neuronal processing within such networks may be found to confer variability in performance, and thus preservation of processing capacity in the face of neuropathological change. Ultimately, it is conceivable that identifying gene variants associated with greater brain reserve can lead to advances in neuro-rehabilitation and pharmacology, as well as furthering our understanding of the biological basis of cognition.

Understanding the inter-individual variation in neurocognitive outcomes and risk for disease associated with genetic variation could advance NeuroAIDS research in a number of ways. First, it may lead to earlier identification of those at risk for HAND, thus allowing prophylactic measures and closer monitoring of medication adherence. Second, consideration of host-genotypic variation may lead to a deeper understanding of etiological factors behind neurocognitive syndromes in those with HIV. A third result may be greater experimental control, as certain GPs have been found to be associated with poorer cognitive functioning and increased risk of psychiatric symptoms. Finally, improved targeting of pharmaceutical and behavioral interventions will be possible as a result of our deepening understanding of the contribution of specific GPs to the neurocognitive consequences of HIV.

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