Published in final edited form as:

AIDS Behav. 2009 February ; 13(1): 118–132. doi:10.1007/s10461-008-9360-x.

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

Andrew J. Levine,

National Neurological AIDS Bank, Department of Neurology, University of California Los Angeles – David Geffen School of Medicine, 11645 Wilshire Blvd., Suite 770, Los Angeles, CA 90025, USA

Elyse J. Singer, and

National Neurological AIDS Bank, Department of Neurology, University of California Los Angeles – David Geffen School of Medicine, 11645 Wilshire Blvd., Suite 770, Los Angeles, CA 90025, USA

Paul Shapshak

Departments of Psychiatry & Behavioral Medicine and Medicine (Division of Infectious Diseases), University of South Florida –College of Medicine, Tampa, FL, USA

Andrew J. Levine: ajlevine@mednet.ucla.edu

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

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

Correspondence to: Andrew J. Levine, ajlevine@mednet.ucla.edu.

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 immunosuppression 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 chemoattractant 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; Edelstein and Knight 1987; Kieburtz et al. 1991; Koutsilieri et al. 2002; Navia et al. 1986). Structural MRI studies of individuals with HAD 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 HAD 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 HAD.

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 frontostriatal 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 frontostriatal 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 frontostriatal 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 HIVE 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 HIVE 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, immunosuppression, 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 comorbidities, and lifestyle behaviors. Ethnicity, for example, may be associated with risk of developing HAND. Data from the National Neurological AIDS Bank cohort, a multiethnic 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 frontostriatal 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 ≥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, macrophagetropic, 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 upregulated 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 (Hesselgesser 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 HIVE 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 upregulates 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 upregulate 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 frontostriatal 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 (Vandenbergh 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 with the 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 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 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 affects 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.

Acknowledgments

Drs. Singer and Levine are supported by NINDS (NS-38841). Dr. Levine is also supported by the California HIV/AIDS Research Program (CHRP) Grant ID06-LA-187. Dr. Shapshak acknowledges support from NIH (GM056529, DA14533, and DA12580).

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
BNDF	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

References

Abraham S, Sweet T, Sawaya BE, Rappaport J, Khalili K, Amini S. Cooperative interaction of C/EBP beta and Tat modulates MCP-1 gene transcription in astrocytes. Journal of Neuroimmunology. 2005; 160(1–2):219–227. [PubMed: 15710476]

Agace WW, Amara A, Roberts AI, Pablos JL, Thelen S, Uguccioni M, Li XY, Marsal J, Arenzana-Seisdedos F, Delaunay T, Ebert EC, Moser B, Parker CM. Constitutive expression of stromal derived factor-1 by mucosal epithelia and its role in HIV transmission and propagation. Current Biology. 2000; 10(6):325–328. [PubMed: 10744978]

Ances BM, Ellis RJ. Dementia and neurocognitive disorders due to HIV-1 infection. Seminars in Neurology. 2007; 27(1):86–92. [PubMed: 17226745]

Anderson E, Zink W, Xiong H, Gendelman HE. HIV-1-associated dementia: A metabolic encephalopathy perpetrated by virus-infected and immune-competent mononuclear phagocytes. Journal of Acquired Immune Deficiency Syndrome. 2002; 31(Suppl 2):S43–54.

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69(18):1789–1799. [PubMed: 17914061]

Arendt G, von Giesen HJ. Human immunodeficiency virus dementia: Evidence of a subcortical process from studies of fine finger movements. Journal of Neurovirology. 2002; 8(Suppl 2):27–32. [PubMed: 12491148]

Asensio VC, Campbell IL. Chemokines in the CNS: Plurifunctional mediators in diverse states. Trends in Neuroscience. 1999; 22(11):504–512.

Avison MJ, Nath A, Greene-Avison R, Schmitt FA, Bales RA, Ethisham A, Greenberg RN, Berger JR. Inflammatory changes and breakdown of microvascular integrity in early human immunodeficiency virus dementia. Journal of Neurovirology. 2004a; 10(4):223–232. [PubMed: 15371152]

Avison MJ, Nath A, Greene-Avison R, Schmitt FA, Greenberg RN, Berger JR. Neuroimaging correlates of HIV-associated BBB compromise. Journal of Neuroimmunology. 2004b; 157(1–2): 140–146. [PubMed: 15579291]

Aylward EH, Henderer JD, McArthur JC, Brettschneider PD, Harris GJ, Barta PE, Pearlson GD. Reduced basal ganglia volume in HIV-1-associated dementia: Results from quantitative neuroimaging. Neurology. 1993; 43(10):2099–2104. [PubMed: 8413973]

Becker JT, Lopez OL, Dew MA, Aizenstein HJ. Prevalence of cognitive disorders differs as a function of age in HIV virus infection. AIDS. 2004; 18(Suppl 1):S11–18. [PubMed: 15075493]

Bell JE. An update on the neuropathology of HIV in the HAART era. Histopathology. 2004; 45(6): 549–559. [PubMed: 15569045]

Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. Nature Genetics. 1996; 12(1):81–84. [PubMed: 8528258]

Bennett BA, Rusyniak DE, Hollingsworth CK. HIV-1 gp120-induced neurotoxicity to midbrain dopamine cultures. Brain Research. 1995; 705(1–2):168–176. [PubMed: 8821747]

Benos DJ, McPherson S, Hahn BH, Chaikin MA, Benveniste EN. Cytokines and HIV envelope glycoprotein gp120 stimulate Na+/H+ exchange in astrocytes. Journal of Biological Chemistry. 1994; 269(19):13811–13816. [PubMed: 8188658]

Berger JR, Kumar M, Kumar A, Fernandez JB, Levin B. Cerebrospinal fluid dopamine in HIV-1 infection. AIDS (8). 1994; (1):67–71. [PubMed: 8011238]

Berger JR, Nath A. HIV dementia and the basal ganglia. Intervirology. 1997; 40(2–3):122–131. [PubMed: 9450229]

Berger JR, Nath A, Greenberg RN, Andersen AH, Greene RA, Bognar A, Avison MJ. Cerebrovascular changes in the basal ganglia with HIV dementia. Neurology. 2000; 54(4):921–926. [PubMed: 10690987]

Bertolino A, Blasi G, Latorre V, Rubino V, Rampino A, Sinibaldi L, Caforio G, Petruzzella V, Pizzuti A, Scarabino T, Nardini M, Weinberger DR, Dallapiccola B. Additive effects of genetic variation

in dopamine regulating genes on working memory cortical activity in human brain. Journal of Neuroscience. 2006; 26(15):3918–3922. [PubMed: 16611807]

Bilder RM, Volavka J, Czobor P, Malhotra AK, Kennedy JL, Ni X, Goldman RS, Hoptman MJ, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, Kunz M, Chakos M, Cooper TB, Lieberman JA. Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. Biological Psychiatry. 2002; 52(7):701–707. [PubMed: 12372660]

Bornstein RA, Nasrallah HA, Para MF, Whitacre CC, Rosenberger P, Fass RJ. Neuropsychological performance in symptomatic and asymptomatic HIV infection. AIDS. 1993; 7(4):519–524. [PubMed: 8507418]

Boven LA, van der Bruggen T, van Asbeck BS, Marx JJ, Nottet HS. Potential role of CCR5 polymorphism in the development of AIDS dementia complex. FEMS Immunology and Medical Microbiology. 1999; 26(3–4):243–247. [PubMed: 10575135]

Brabers NA, Nottet HS. Role of the pro-inflammatory cytokines TNF-alpha and IL-1beta in HIV-associated dementia. European Journal of Clinical Investigation. 2006; 36(7):447–458. [PubMed: 16796601]

Cartier L, Hartley O, Dubois-Dauphin M, Krause KH. Chemokine receptors in the central nervous system: Role in brain inflammation and neurodegenerative diseases. Brain Research Brain Research Reviews. 2005; 48(1):16–42. [PubMed: 15708626]

Chang L, Tomasi D, Yakupov R, Lozar C, Arnold S, Caparelli E, Ernst T. Adaptation of the attention network in human immunodeficiency virus brain injury. Annals of Neurology. 2004; 56(2):259–272. [PubMed: 15293278]

Chao CC, Hu S. Tumor necrosis factor-alpha potentiates glutamate neurotoxicity in human fetal brain cell cultures. Developmental Neuroscience. 1994; 16(3–4):172–179. [PubMed: 7705222]

Cherner M, Ellis RJ, Lazzaretto D, Young C, Mindt MR, Atkinson JH, Grant I, Heaton RK. Effects of HIV-1 infection and aging on neurobehavioral functioning: Preliminary findings. AIDS. 2004; 18(Suppl 1):S27–34. [PubMed: 15075495]

Cherner M, Letendre S, Heaton RK, Durelle J, Marquie-Beck J, Gragg B, Grant I. Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. Neurology. 2005; 64(8):1343–1347. [PubMed: 15851720]

Cherner M, Masliah E, Ellis RJ, Marcotte TD, Moore DJ, Grant I, Heaton RK. Neurocognitive dysfunction predicts postmortem findings of HIV encephalitis. Neurology. 2002; 59(10):1563–1567. [PubMed: 12451198]

Clements JE, Li M, Gama L, Bullock B, Carruth LM, Mankowski JL, Zink MC. The central nervous system is a viral reservoir in simian immunodeficiency virus-infected macaques on combined antiretroviral therapy: A model for human immunodeficiency virus patients on highly active antiretroviral therapy. Journal of Neurovirology. 2005; 11(2):180–189. [PubMed: 16036796]

Cocchi F, DeVico AL, Garzino-Demo A, Arya SK, Gallo RC, Lusso P. Identification of RANTES, MIP-1 alpha, and MIP-1 beta as the major HIV-suppressive factors produced by CD8+ T cells. Science. 1995; 270(5243):1811–1815. [PubMed: 8525373]

Corder EH, Robertson K, Lannfelt L, Bogdanovic N, Eggertsen G, Wilkins J, Hall C. HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. Nature Medicine. 1998; 4(10):1182–1184.

Cysique LA, Maruff P, Brew BJ. Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: A combined study of two cohorts. Journal of Neurovirology. 2004; 10(6):350–357. [PubMed: 15765806]

D'Hooge R, Franck F, Mucke L, De Deyn PP. Age-related behavioural deficits in transgenic mice expressing the HIV-1 coat protein gp120. European Journal of Neuroscience. 1999; 11(12):4398–4402. [PubMed: 10594667]

Dal Pan GJ, McArthur JH, Aylward E, Selnes OA, Nance-Sproson TE, Kumar AJ, Mellits ED, McArthur JC. Patterns of cerebral atrophy in HIV-1-infected individuals: Results of a quantitative MRI analysis. Neurology. 1992; 42(11):2125–2130. [PubMed: 1436522]

Daly G, Hawi Z, Fitzgerald M, Gill M. Mapping susceptibility loci in attention deficit hyperactivity disorder: Preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. Molecular Psychiatry. 1999; 4(2):192–196. [PubMed: 10208453]

Diaz-Arrastia R, Gong Y, Kelly CJ, Gelman BB. Host genetic polymorphisms in human immunodeficiency virus-related neurologic disease. Journal of Neurovirology. 2004; 10(Suppl 1): 67–73. [PubMed: 14982742]

Do H, Vasilescu A, Carpentier W, Meyer L, Diop G, Hirtzig T, Coulonges C, Labib T, Spadoni JL, Therwath A, Lathrop M, Matsuda F, Zagury JF. Exhaustive genotyping of the interleukin-1 family genes and associations with AIDS progression in a French cohort. Journal of Infectious Diseases. 2006; 194(11):1492–1504. [PubMed: 17083033]

Dore GJ, McDonald A, Li Y, Kaldor JM, Brew BJ. Marked improvement in survival following AIDS dementia complex in the era of highly active antiretroviral therapy. AIDS. 2003; 17(10):1539–1545. [PubMed: 12824792]

Dragic T, Litwin V, Allaway GP, Martin SR, Huang Y, Nagashima KA, Cayanan C, Maddon PJ, Koup RA, Moore JP, Paxton WA. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. Nature. 1996; 381(6584):667–673. [PubMed: 8649512]

Edelstein H, Knight RT. Severe parkinsonism in two AIDS patients taking prochlorperazine. Lancet. 1987; 2(8554):341–342. [PubMed: 2886808]

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98(12):6917–6922. [PubMed: 11381111]

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003; 112(2): 257–269. [PubMed: 12553913]

El-Hage N, Wu G, Wang J, Ambati J, Knapp PE, Reed JL, Bruce-Keller AJ, Hauser KF. HIV-1 Tat and opiate-induced changes in astrocytes promote chemotaxis of microglia through the expression of MCP-1 and alternative chemokines. Glia. 2006; 53(2):132–146. [PubMed: 16206161]

Engelmayer J, Larsson M, Lee A, Lee M, Cox WI, Steinman RM, Bhardwaj N. Mature dendritic cells infected with canarypox virus elicit strong anti-human immunodeficiency virus CD8+ and CD4+ T-cell responses from chronically infected individuals. Journal of Virology. 2001; 75(5):2142–2153. [PubMed: 11160718]

Ernst T, Chang L, Leonido-Yee M, Speck O. Evidence for long-term neurotoxicity associated with methamphetamine abuse: A 1H MRS study. Neurology. 2000; 54(6):1344–1349. [PubMed: 10746608]

Falangola MF, Hanly A, Galvao-Castro B, Petito CK. HIV infection of human choroid plexus: A possible mechanism of viral entry into the CNS. Journal of Neuropathology and Experimental Neurology. 1995; 54(4):497–503. [PubMed: 7602324]

Fellay J, Shianna KV, Ge D, Colombo S, Ledergerber B, Weale M, Zhang K, Gumbs C, Castagna A, Cossarizza A, Cozzi-Lepri A, De Luca A, Easterbrook P, Francioli P, Mallal S, Martinez-Picado J, Miro JM, Obel N, Smith JP, Wyniger J, Descombes P, Antonarakis SE, Letvin NL, McMichael AJ, Haynes BF, Telenti A, Goldstein DB. A whole-genome association study of major determinants for host control of HIV-1. Science. 2007; 317(5840):944–947. [PubMed: 17641165]

Freimer NB, Sabatti C. Human genetics: Variants in common diseases. Nature. 2007; 445(7130):828–830. [PubMed: 17293879]

Galea I, Bechmann I, Perry VH. What is immune privilege (not)? Trends in Immunology. 2007; 28(1): 12–18. [PubMed: 17129764]

Gartner S. HIV infection and dementia. Science. 2000; 287(5453):602–604. [PubMed: 10691542]

Gelbard HA, Nottet HS, Swindells S, Jett M, Dzenko KA, Genis P, White R, Wang L, Choi YB, Zhang D, et al. Platelet-activating factor: A candidate human immunodeficiency virus type 1-induced neurotoxin. Journal of Virology. 1994; 68(7):4628–4635. [PubMed: 8207837]

Gendelman HE, Orenstein JM, Baca LM, Weiser B, Burger H, Kalter DC, Meltzer MS. The macrophage in the persistence and pathogenesis of HIV infection. AIDS. 1989; 3(8):475–495. [PubMed: 2508709]

Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR. Executive subprocesses in working memory: Relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Archives of General Psychiatry. 2003; 60(9):889–896. [PubMed: 12963670]

Gonzalez E, Dhanda R, Bamshad M, Mummidi S, Geevarghese R, Catano G, Anderson SA, Walter EA, Stephan KT, Hammer MF, Mangano A, Sen L, Clark RA, Ahuja SS, Dolan MJ, Ahuja SK. Global survey of genetic variation in CCR5, RANTES, and MIP-1alpha: Impact on the epidemiology of the HIV-1 pandemic. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98(9):5199–5204. [PubMed: 11320252]

Gonzalez E, Rovin BH, Sen L, Cooke G, Dhanda R, Mummidi S, Kulkarni H, Bamshad MJ, Telles V, Anderson SA, Walter EA, Stephan KT, Deucher M, Mangano A, Bologna R, Ahuja SS, Dolan MJ, Ahuja SK. HIV-1 infection and AIDS dementia are influenced by a mutant MCP-1 allele linked to increased monocyte infiltration of tissues and MCP-1 levels. Proceedings of the National Academy of Sciences of the United States of America. 2002; 99(21):13795–13800. [PubMed: 12374865]

Goplen AK, Liestol K, Dunlop O, Bruun JN, Maehlen J. Dementia in AIDS patients in Oslo; the role of HIV encephalitis and CMV encephalitis. Scandinavian Journal of Infectious Diseases. 2001; 33(10):755–758. [PubMed: 11728043]

Gray F, Chretien F, Vallat-Decouvelaere AV, Scaravilli F. The changing pattern of HIV neuropathology in the HAART era. Journal of Neuropathology and Experimental Neurology. 2003; 62(5):429–440. [PubMed: 12769183]

Guillin O, Diaz J, Carroll P, Griffon N, Schwartz JC, Sokoloff P. BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. Nature. 2001; 411(6833):86–89. [PubMed: 11333982]

Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, Egan MF, Weinberger DR. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. Journal of Neuroscience. 2003; 23(17):6690–6694. [PubMed: 12890761]

He J, Chen Y, Farzan M, Choe H, Ohagen A, Gartner S, Busciglio J, Yang X, Hofmann W, Newman W, Mackay CR, Sodroski J, Gabuzda D. CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia. Nature. 1997; 385(6617):645–649. [PubMed: 9024664]

Hesselgesser J, Taub D, Baskar P, Greenberg M, Hoxie J, Kolson DL, Horuk R. Neuronal apoptosis induced by HIV-1 gp120 and the chemokine SDF-1 alpha is mediated by the chemokine receptor CXCR4. Current Biology. 1998; 8(10):595–598. [PubMed: 9601645]

Hinkin CH, van Gorp WG, Mandelkern MA, Gee M, Satz P, Holston S, Marcotte TD, Evans G, Paz DH, Ropchan JR, et al. Cerebral metabolic change in patients with AIDS: Report of a six-month follow-up using positron-emission tomography. Journal of Neuropsychiatry and Clinical Neurosciences. 1995; 7(2):180–187. [PubMed: 7626961]

Hirvonen M, Laakso A, Nagren K, Rinne JO, Pohjalainen T, Hietala J. C957T polymorphism of the dopamine D2 receptor (DRD2) gene affects striatal DRD2 availability in vivo. Molecular Psychiatry. 2004; 9(12):1060–1061. [PubMed: 15278099]

Itoh K, Mehraein P, Weis S. Neuronal damage of the substantia nigra in HIV-1 infected brains. Acta Neuropathological (Berlin). 2000; 99(4):376–384.

Jacobsen LK, Giedd JN, Gottschalk C, Kosten TR, Krystal JH. Quantitative morphology of the caudate and putamen in patients with cocaine dependence. American Journal of Psychiatry. 2001; 158(3):486–489. [PubMed: 11229995]

Jones M, Olafson K, Del Bigio MR, Peeling J, Nath A. Intraventricular injection of human immunodeficiency virus type 1 (HIV-1) tat protein causes inflammation, gliosis, apoptosis, and ventricular enlargement. Journal of Neuropathology and Experimental Neurology. 1998; 57(6): 563–570. [PubMed: 9630236]

Kaul M, Lipton SA. Chemokines and activated macrophages in HIV gp120-induced neuronal apoptosis. Proceedings of the National Academy of Sciences of the United States of America. 1999; 96(14):8212–8216. [PubMed: 10393974]

Kaul M, Zheng J, Okamoto S, Gendelman HE, Lipton SA. HIV-1 infection and AIDS: Consequences for the central nervous system. Cell Death and Differentiation. 2005; 12(Suppl 1):878–892. [PubMed: 15832177]

Kieburtz KD, Epstein LG, Gelbard HA, Greenamyre JT. Excitotoxicity and dopaminergic dysfunction in the acquired immunodeficiency syndrome dementia complex. Therapeutic implications. Archives of Neurology. 1991; 48(12):1281–1284. [PubMed: 1845034]

Koutsilieri E, Sopper S, Scheller C, ter Meulen V, Riederer P. Parkinsonism in HIV dementia. Journal of Neural Transmission. 2002; 109(5–6):767–775. [PubMed: 12111466]

Kramer-Hammerle S, Rothenaigner I, Wolff H, Bell JE, Brack-Werner R. Cells of the central nervous system as targets and reservoirs of the human immunodeficiency virus. Virus Research. 2005; 111(2):194–213. [PubMed: 15885841]

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics. 1996; 6(3):243–250. [PubMed: 8807664]

Langford TD, Letendre SL, Larrea GJ, Masliah E. Changing patterns in the neuropathogenesis of HIV during the HAART era. Brain Pathology. 2003; 13(2):195–210. [PubMed: 12744473]

Larsson M, Hagberg L, Forsman A, Norkrans G. Cerebrospinal fluid catecholamine metabolites in HIV-infected patients. Journal of Neuroscience Research. 1991; 28(3):406–409. [PubMed: 1856886]

Levine AJ, Hardy DJ, Miller E, Castellon SA, Longshore D, Hinkin CH. The effect of recent stimulant use on sustained attention in HIV-infected adults. Journal of Clinical and Experimental Neuropsychology. 2006; 28(1):29–42. [PubMed: 16448974]

Li T, Chen CK, Hu X, Ball D, Lin SK, Chen W, Sham PC, Loh el W, Murray RM, Collier DA. Association analysis of the DRD4 and COMT genes in methamphetamine abuse. American Journal of Medical Genetics Part B, Neuropsychiatric Genetics. 2004; 129(1):120–124.

Lichter JB, Barr CL, Kennedy JL, Van Tol HH, Kidd KK, Livak KJ. A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. Human Molecular Genetics. 1993; 2(6):767–773. [PubMed: 8353495]

Little KY, Zhang L, Desmond T, Frey KA, Dalack GW, Cassin BJ. Striatal dopaminergic abnormalities in human cocaine users. American Journal of Psychiatry. 1999; 156(2):238–245. [PubMed: 9989560]

Liu H, Chao D, Nakayama EE, Taguchi H, Goto M, Xin X, Takamatsu JK, Saito H, Ishikawa Y, Akaza T, Juji T, Takebe Y, Ohishi T, Fukutake K, Maruyama Y, Yashiki S, Sonoda S, Nakamura T, Nagai Y, Iwamoto A, Shioda T. Polymorphism in RANTES chemokine promoter affects HIV-1 disease progression. Proceedings of the National Academy of Sciences of the United States of America. 1999; 96(8):4581–4585. [PubMed: 10200305]

Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. American Journal of Psychiatry. 2002; 159(4):652–654. [PubMed: 11925305]

Maslin CL, Kedzierska K, Webster NL, Muller WA, Crowe SM. Transendothelial migration of monocytes: The underlying molecular mechanisms and consequences of HIV-1 infection. Current HIV Research. 2005; 3(4):303–317. [PubMed: 16250878]

Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proceedings of the National Academy of Sciences of the United States of America. 2003; 100(10):6186–6191. [PubMed: 12716966]

Mattson MP, Haughey NJ, Nath A. Cell death in HIV dementia. Cell Death and Differentiation. 2005; 12(Suppl 1):893–904. [PubMed: 15761472]

McDermott DH, Beecroft MJ, Kleeberger CA, Al-Sharif FM, Ollier WE, Zimmerman PA, Boatin BA, Leitman SF, Detels R, Hajeer AH, Murphy PM. Chemokine RANTES promoter polymorphism

affects risk of both HIV infection and disease progression in the Multicenter AIDS Cohort Study. AIDS. 2000; 14(17):2671–2678. [PubMed: 11125885]

Meucci O, Fatatis A, Simen AA, Bushell TJ, Gray PW, Miller RJ. Chemokines regulate hippocampal neuronal signaling and gp120 neurotoxicity. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95(24):14500–14505. [PubMed: 9826729]

Meyer-Lindenberg A, Straub RE, Lipska BK, Verchinski BA, Goldberg T, Callicott JH, Egan MF, Huffaker SS, Mattay VS, Kolachana B, Kleinman JE, Weinberger DR. Genetic evidence implicating DARPP-32 in human frontostriatal structure, function, and cognition. Journal of Clinical Investigation. 2007; 117(3):672–682. [PubMed: 17290303]

Meyer L, Magierowska M, Hubert JB, Rouzioux C, Deveau C, Sanson F, Debre P, Delfraissy JF, Theodorou I. Early protective effect of CCR-5 delta 32 heterozygosity on HIV-1 disease progression: Relationship with viral load. The SEROCO Study Group. AIDS. 1997; 11(11):F73–78. [PubMed: 9302436]

Michael NL, Moore JP. HIV-1 entry inhibitors: Evading the issue. Nature Medicine. 1999; 5(7):740–742.

Mill J, Fisher N, Curran S, Richards S, Taylor E, Asherson P. Polymorphisms in the dopamine D4 receptor gene and attention-deficit hyperactivity disorder. Neuroreport. 2003; 14(11):1463–1466. [PubMed: 12960764]

Mossner R, Daniel S, Albert D, Heils A, Okladnova O, Schmitt A, Lesch KP. Serotonin transporter function is modulated by brain-derived neurotrophic factor (BDNF) but not nerve growth factor (NGF). Neurochemistry International. 2000; 36(3):197–202. [PubMed: 10676853]

Nath A, Geiger J. Neurobiological aspects of human immunodeficiency virus infection: Neurotoxic mechanisms. Progress in Neurobiology. 1998; 54(1):19–33. [PubMed: 9460791]

Nath A, Haughey NJ, Jones M, Anderson C, Bell JE, Geiger JD. Synergistic neurotoxicity by human immunodeficiency virus proteins Tat and gp120: Protection by memantine. Annals of Neurology. 2000; 47(2):186–194. [PubMed: 10665489]

Nath A, Maragos WF, Avison MJ, Schmitt FA, Berger JR. Acceleration of HIV dementia with methamphetamine and cocaine. Journal of Neurovirology. 2001; 7(1):66–71. [PubMed: 11519485]

Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. Annals of Neurology. 1986; 19(6):517–524. [PubMed: 3729308]

Navia BA, Price RW. The acquired immunodeficiency syndrome dementia complex as the presenting or sole manifestation of human immunodeficiency virus infection. Archives of Neurology. 1987; 44(1):65–69. [PubMed: 3800724]

Neuenburg JK, Brodt HR, Herndier BG, Bickel M, Bacchetti P, Price RW, Grant RM, Schlote W. HIV-related neuropathology, 1985 to 1999: Rising prevalence of HIV encephalopathy in the era of highly active antiretroviral therapy. Journal of Acquired Immune Deficiency Syndrome. 2002; 31(2):171–177.

Nolan KA, Bilder RM, Lachman HM, Volavka J. Catechol O-methyltransferase Val158Met polymorphism in schizophrenia: Differential effects of Val and Met alleles on cognitive stability and flexibility. American Journal of Psychiatry. 2004; 161(2):359–361. [PubMed: 14754787]

Nosheny RL, Mocchetti I, Bachis A. Brain-derived neurotrophic factor as a prototype neuroprotective factor against HIV-1-associated neuronal degeneration. Neurotoxicology Research. 2005; 8(1–2): 187–198.

Ouimet CC, LaMantia AS, Goldman-Rakic P, Rakic P, Greengard P. Immunocytochemical localization of DARPP-32, a dopamine and cyclic-AMP-regulated phosphoprotein, in the primate brain. Journal of Comparative Neurology. 1992; 323(2):209–218. [PubMed: 1328330]

Palmer DL, Hjelle BL, Wiley CA, Allen S, Wachsman W, Mills RG, Davis LE, Merlin TL. HIV-1 infection despite immediate combination antiviral therapy after infusion of contaminated white cells. American Journal of Medicine. 1994; 97(3):289–295. [PubMed: 8092178]

Peng H, Erdmann N, Whitney N, Dou H, Gorantla S, Gendelman HE, Ghorpade A, Zheng J. HIV-1-infected and/or immune activated macrophages regulate astrocyte SDF-1 production through IL-1beta. Glia. 2006; 54(6):619–629. [PubMed: 16944452]

Persidsky Y, Gendelman HE. Mononuclear phagocyte immunity and the neuropathogenesis of HIV-1 infection. Journal of Leukocyte Biology. 2003; 74(5):691–701. [PubMed: 14595004]

Persidsky Y, Poluektova L. Immune privilege and HIV-1 persistence in the CNS. Immunology Review. 2006; 213:180–194.

Persidsky Y, Stins M, Way D, Witte MH, Weinand M, Kim KS, Bock P, Gendelman HE, Fiala M. A model for monocyte migration through the blood–brain barrier during HIV-1 encephalitis. Journal of Immunology. 1997; 158(7):3499–3510.

Persidsky Y, Zheng J, Miller D, Gendelman HE. Mononuclear phagocytes mediate blood–brain barrier compromise and neuronal injury during HIV-1-associated dementia. Journal of Leukocyte Biology. 2000; 68(3):413–422. [PubMed: 10985259]

Petito CK. Human immunodeficiency virus type 1 compartmentalization in the central nervous system. Journal of Neurovirology. 2004; 10(Suppl 1):21–24. [PubMed: 14982735]

Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. Journal of Neuroscience. 2004; 24(45):10099–10102. [PubMed: 15537879]

Plomin, R.; DeFries, JC.; McClearn, GE.; McGuffin, P. Behavioral genetics. 4. New York: Worth Publishers; 2001.

Power C, Kong PA, Crawford TO, Wesselingh S, Glass JD, McArthur JC, Trapp BD. Cerebral white matter changes in acquired immunodeficiency syndrome dementia: Alterations of the blood–brain barrier. Annals of Neurology. 1993; 34(3):339–350. [PubMed: 7689819]

Price P, James I, Fernandez S, French MA. Alleles of the gene encoding IL-1alpha may predict control of plasma viraemia in HIV-1 patients on highly active antiretroviral therapy. AIDS. 2004; 18(11):1495–1501. [PubMed: 15238767]

Puissant B, Roubinet F, Massip P, Sandres-Saune K, Apoil PA, Abbal M, Pasquier C, Izopet J, Blancher A. Analysis of CCR5, CCR2, CX3CR1, and SDF1 polymorphisms in HIV-positive treated patients: Impact on response to HAART and on peripheral T lymphocyte counts. AIDS Research and Human Retroviruses. 2006; 22(2):153–162. [PubMed: 16478397]

Quasney MW, Zhang Q, Sargent S, Mynatt M, Glass J, McArthur J. Increased frequency of the tumor necrosis factor-alpha-308 A allele in adults with human immunodeficiency virus dementia. Annals of Neurology. 2001; 50(2):157–162. [PubMed: 11506397]

Qureshi AI, Hanson DL, Jones JL, Janssen RS. Estimation of the temporal probability of human immunodeficiency virus (HIV) dementia after risk stratification for HIV-infected persons. Neurology. 1998; 50(2):392–397. [PubMed: 9484360]

Ragin AB, Wu Y, Storey P, Cohen BA, Edelman RR, Epstein LG. Monocyte chemoattractant protein-1 correlates with subcortical brain injury in HIV infection. Neurology. 2006; 66(8):1255–1257. [PubMed: 16636247]

Resnick L, diMarzo-Veronese F, Schupbach J, Tourtellotte WW, Ho DD, Muller F, Shapshak P, Vogt M, Groopman JE, Markham PD, et al. Intra-blood–brain-barrier synthesis of HTLV-III-specific IgG in patients with neurologic symptoms associated with AIDS or AIDS-related complex. New England Journal of Medicine. 1985; 313(24):1498–1504. [PubMed: 2999592]

Rippeth JD, Heaton RK, Carey CL, Marcotte TD, Moore DJ, Gonzalez R, Wolfson T, Grant I. Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. Journal of the International Neuropsychological Society. 2004; 10(1):1–14. [PubMed: 14751002]

Rogers G, Joyce P, Mulder R, Sellman D, Miller A, Allington M, Olds R, Wells E, Kennedy M. Association of a duplicated repeat polymorphism in the 5′-untranslated region of the DRD4 gene with novelty seeking. American Journal of Medical Genetics: Part B, Neuropsychiatric Genetics. 2004; 126(1):95–98.

Roman T, Schmitz M, Polanczyk GV, Eizirik M, Rohde LA, Hutz MH. Further evidence for the association between attention-deficit/hyperactivity disorder and the dopamine-beta-hydroxylase gene. American Journal of Medical Geneticst. 2002; 114(2):154–158.

Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martinez-Larrea A, Fananas L. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. American Journal of Psychiatry. 2004; 161(6):1110–1112. [PubMed: 15169701]

Rottenberg DA, Sidtis JJ, Strother SC, Schaper KA, Anderson JR, Nelson MJ, Price RW. Abnormal cerebral glucose metabolism in HIV-1 seropositive subjects with and without dementia. Journal of Nuclear Medicine. 1996; 37(7):1133–1141. [PubMed: 8965184]

Rovin BH, Lu L, Saxena R. A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. Biochemical and Biophysical Research Communications. 1999; 259(2):344–348. [PubMed: 10362511]

Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, Saragosti S, Lapoumeroulie C, Cognaux J, Forceille C, Muyldermans G, Verhofstede C, Burtonboy G, Georges M, Imai T, Rana S, Yi Y, Smyth RJ, Collman RG, Doms RW, Vassart G, Parmentier M. Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature. 1996; 382(6593):722–725. [PubMed: 8751444]

Sardar AM, Czudek C, Reynolds GP. Dopamine deficits in the brain: The neurochemical basis of parkinsonian symptoms in AIDS. Neuroreport. 1996; 7(4):910–912. [PubMed: 8724671]

Satz P, Morgenstern H, Miller EN, Selnes OA, McArthur JC, Cohen BA, Wesch J, Becker JT, Jacobson L, D'Elia LF, et al. Low education as a possible risk factor for cognitive abnormalities in HIV-1: Findings from the multicenter AIDS Cohort Study (MACS). Journal of the Acquired Immune Deficiency Syndrome. 1993; 6(5):503–511.

Selmaj K, Raine CS. Tumor necrosis factor mediates myelin damage in organotypic cultures of nervous tissue. Annals of the New York Academy of Sciences. 1988; 540:568–570. [PubMed: 2462832]

Shapshak P, Segal DM, Crandall KA, Fujimura RK, Zhang BT, Xin KQ, Okuda K, Petito CK, Eisdorfer C, Goodkin K. Independent evolution of HIV type 1 in different brain regions. AIDS Research and Human Retroviruses. 1999; 15(9):811–820. [PubMed: 10381169]

Shapshak P, Yoshioka M, Sun NC, Schiller PC. The use of combined in situ hybridization and immunocytochemistry to identify HIV-infected cells in brain tissue. Modern Pathology. 1992; 5(6):649–654. [PubMed: 1369802]

Shrestha S, Strathdee SA, Galai N, Oleksyk T, Fallin MD, Mehta S, Schaid D, Vlahov D, O'Brien SJ, Smith MW. Behavioral risk exposure and host genetics of susceptibility to HIV-1 infection. Journal of Infectious Diseases. 2006; 193(1):16–26. [PubMed: 16323127]

Singh KK, Barroga CF, Hughes MD, Chen J, Raskino C, McKinney RE, Spector SA. Genetic influence of CCR5, CCR2, and SDF1 variants on human immunodeficiency virus 1 (HIV-1)-related disease progression and neurological impairment, in children with symptomatic HIV-1 infection. Journal of Infectious Diseases. 2003; 188(10):1461–1472. [PubMed: 14624371]

Singh KK, Ellis RJ, Marquie-Beck J, Letendre S, Heaton RK, Grant I, Spector SA. CCR2 polymorphisms affect neuropsychological impairment in HIV-1-infected adults. Journal of Neuroimmunology. 2004; 157(1–2):185–192. [PubMed: 15579296]

Smalley SL, Bailey JN, Palmer CG, Cantwell DP, McGough JJ, Del'Homme MA, Asarnow JR, Woodward JA, Ramsey C, Nelson SF. Evidence that the dopamine D4 receptor is a susceptibility gene in attention deficit hyperactivity disorder. Molecular Psychiatry. 1998; 3(5):427–430. [PubMed: 9774776]

Smit TK, Brew BJ, Tourtellotte W, Morgello S, Gelman BB, Saksena NK. Independent evolution of human immunodeficiency virus (HIV) drug resistance mutations in diverse areas of the brain in HIV-infected patients, with and without dementia, on antiretroviral treatment. Journal of Virology. 2004; 78(18):10133–10148. [PubMed: 15331746]

Smith MW, Dean M, Carrington M, Winkler C, Huttley GA, Lomb DA, Goedert JJ, O'Brien TR, Jacobson LP, Kaslow R, Buchbinder S, Vittinghoff E, Vlahov D, Hoots K, Hilgartner MW, O'Brien SJ. Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC), ALIVE Study. Science. 1997; 277(5328):959–965. [PubMed: 9252328]

Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. Journal of the International Neuropsychological Society. 2002; 8(3):448–460. [PubMed: 11939702]

Thapar A, Harold G, Rice F, Langley K, O'donovan M. The contribution of gene–environment interaction to psychopathology. Developmental Psychopathology. 2007; 19(4):989–1004.

Thomas SA. Anti-HIV drug distribution to the central nervous system. Current Pharmaceutical Design. 2004; 10(12):1313–1324. [PubMed: 15134483]

Tomasi D, Chang L, de Castro Caparelli E, Telang F, Ernst T. The human immunodeficiency virus reduces network capacity: Acoustic noise effect. Annals of Neurology. 2006; 59(2):419–423. [PubMed: 16437575]

Tozzi V, Balestra P, Lorenzini P, Bellagamba R, Galgani S, Corpolongo A, Vlassi C, Larussa D, Zaccarelli M, Noto P, Visco-Comandini U, Giulianelli M, Ippolito G, Antinori A, Narciso P. Prevalence and risk factors for human immunodeficiency virus-associated neurocognitive impairment, 1996 to 2002: Results from an urban observational cohort. Journal of Neurovirology. 2005; 11(3):265–273. [PubMed: 16036806]

Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes OA, Grove J, Liu Y, Abdul-Majid KB, Gartner S, Sacktor N. Age, apolipoprotein E4, and the risk of HIV dementia: The Hawaii aging with HIV cohort. Journal of Neuroimmunology. 2004; 157(1–2):197–202. [PubMed: 15579298]

Valcour V, Shikuma C, Shiramizu B, Williams A, Watters M, Poff P, Grove J, Selnes O, Sacktor N. Diabetes, insulin resistance, and dementia among HIV-1-infected patients. Journal of the Acquired Immune Deficiency Syndrome. 2005; 38(1):31–36.

Valcour V, Shikuma C, Watters M, Sacktor N. Cognitive impairment in older HIV-1-seropositive individuals: Prevalence and potential mechanisms. AIDS. 2004; 18(Suppl 1):S79–86. [PubMed: 15075502]

van Gorp WG, Mandelkern MA, Gee M, Hinkin CH, Stern CE, Paz DK, Dixon W, Evans G, Flynn F, Frederick CJ, et al. Cerebral metabolic dysfunction in AIDS: Findings in a sample with and without dementia. Journal of Neuropsychiatry and Clinical Neurosciences. 1992; 4(3):280–287. [PubMed: 1498579]

van Rij RP, Portegies P, Hallaby T, Lange JM, Visser J, de Roda Husman AM, van't Wout AB, Schuitemaker H. Reduced prevalence of the CCR5 delta32 heterozygous genotype in human immunodeficiency virus-infected individuals with AIDS dementia complex. Journal of Infectious Diseases. 1999; 180(3):854–857. [PubMed: 10438379]

Vandenbergh DJ, Persico AM, Hawkins AL, Griffin CA, Li X, Jabs EW, Uhl GR. Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. Genomics. 1992; 14(4):1104–1106. [PubMed: 1478653]

Volkow ND, Chang L, Wang GJ, Fowler JS, Leonido-Yee M, Franceschi D, Sedler MJ, Gatley SJ, Hitzemann R, Ding YS, Logan J, Wong C, Miller EN. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. American Journal of Psychiatry. 2001; 158(3):377–382. [PubMed: 11229977]

Wang GJ, Chang L, Volkow ND, Telang F, Logan J, Ernst T, Fowler JS. Decreased brain dopaminergic transporters in HIV-associated dementia patients. Brain. 2004; 127(Pt 11):2452–2458. [PubMed: 15319273]

Wei J, Xu HM, Ramchand CN, Hemmings GP. Is the polymorphic microsatellite repeat of the dopamine beta-hydroxylase gene associated with biochemical variability of the catecholamine pathway in schizophrenia? Biological Psychiatry. 1997; 41(7):762–767. [PubMed: 9084894]

Weissman D, Dybul M, Daucher MB, Davey RT Jr, Walker RE, Kovacs JA. Interleukin-2 upregulates expression of the human immunodeficiency virus fusion core-ceptor CCR5 by CD4+ lymphocytes in vivo. Journal of Infectious Diseases. 2000; 181(3):933–938. [PubMed: 10720515]

Wesselingh SL, Takahashi K, Glass JD, McArthur JC, Griffin JW, Griffin DE. Cellular localization of tumor necrosis factor mRNA in neurological tissue from HIV-infected patients by combined reverse transcriptase/polymerase chain reaction in situ hybridization and immunohistochemistry. Journal of Neuroimmunology. 1997; 74(1–2):1–8. [PubMed: 9119960]

Wiley CA, Nelson JA. Human immunodeficiency virus: Infection of the nervous system. Current Topics in Microbiology and Immunology. 1990; 160:157–172. [PubMed: 2162284]

Wiley CA, Schrier RD, Nelson JA, Lampert PW, Oldstone MB. Cellular localization of human immunodeficiency virus infection within the brains of acquired immune deficiency syndrome patients. Proceedings of the National Academy of Sciences of the United States of America. 1986; 83(18):7089–7093. [PubMed: 3018755]

Winkler C, Modi W, Smith MW, Nelson GW, Wu X, Carrington M, Dean M, Honjo T, Tashiro K, Yabe D, Buchbinder S, Vittinghoff E, Goedert JJ, O'Brien TR, Jacobson LP, Detels R, Donfield S, Willoughby A, Gomperts E, Vlahov D, Phair J, O'Brien SJ. Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant. ALIVE Study, Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC). Science. 1998; 279(5349):389–393. [PubMed: 9430590]

Wojna V, Skolasky RL, Hechavarria R, Mayo R, Selnes O, McArthur JC, Melendez LM, Maldonado E, Zorrilla CD, Garcia H, Kraiselburd E, Nath A. Prevalence of human immunodeficiency virus-associated cognitive impairment in a group of Hispanic women at risk for neurological impairment. Journal of Neurovirology. 2006; 12(5):356–364. [PubMed: 17065128]

Xu H, Kellendonk CB, Simpson EH, Keilp JG, Bruder GE, Polan HJ, Kandel ER, Gilliam TC. DRD2 C957T polymorphism interacts with the COMT Val158Met polymorphism in human working memory ability. Schizophrenia Research. 2007; 90(1–3):104–107. [PubMed: 17113268]

Yeh MW, Kaul M, Zheng J, Nottet HS, Thylin M, Gendelman HE, Lipton SA. Cytokine-stimulated, but not HIV-infected, human monocyte-derived macrophages produce neurotoxic levels of l-cysteine. Journal of Immunology. 2000; 164(8):4265–4270.

Yoshioka M, Shapshak P, Sun NC, Nelson SJ, Svenningsson A, Tate LG, Pardo V, Resnick L. Simultaneous detection of ferritin and HIV-1 in reactive microglia. Acta Neuropathologica (Berlin). 1992; 84(3):297–306. [PubMed: 1414282]

Zabetian CP, Anderson GM, Buxbaum SG, Elston RC, Ichinose H, Nagatsu T, Kim KS, Kim CH, Malison RT, Gelernter J, Cubells JF. A quantitative-trait analysis of human plasma-dopamine beta-hydroxylase activity: Evidence for a major functional polymorphism at the DBH locus. American Journal of Human Genetics. 2001; 68(2):515–522. [PubMed: 11170900]

Zhang H, Ozbay F, Lappalainen J, Kranzler HR, van Dyck CH, Charney DS, Price LH, Southwick S, Yang BZ, Rasmussen A, Gelernter J. Brain derived neurotrophic factor (BDNF) gene variants and Alzheimer's disease, affective disorders, posttraumatic stress disorder, schizophrenia, and substance dependence. American Journal of Medical Genetics: Part B, Neuropsychiatric Genetics. 2006; 141(4):387–393.

Zheng J, Thylin MR, Ghorpade A, Xiong H, Persidsky Y, Cotter R, Niemann D, Che M, Zeng YC, Gelbard HA, Shepard RB, Swartz JM, Gendelman HE. Intracellular CXCR4 signaling, neuronal apoptosis and neuropathogenic mechanisms of HIV-1-associated dementia. Journal of Neuroimmunology. 1999; 98(2):185–200. [PubMed: 10430052]