

The role of herpesvirus 6A and 6B in multiple sclerosis and epilepsy

Nicky Dunn^{1,2}  | Nastya Kharlamova^{1,2} | Anna Fogdell-Hahn^{1,2} 

¹Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

²Center for Molecular Medicine, Stockholm, Sweden

Correspondence

Anna Fogdell-Hahn, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm SE-171 76, Sweden.
Email: Anna.Fogdell-Hahn@ki.se

Abstract

Human herpesvirus 6A (HHV-6A) and 6B (HHV-6B) are two closely related viruses that can infect cells of the central nervous system (CNS). The similarities between these viruses have made it difficult to separate them on serological level. The broad term HHV-6 remains when referring to studies where the two species were not distinguished, and as such, the seroprevalence is over 90% in the adult population. HHV-6B has been detected in up to 100% of infants with the primary infection roseola infantum, but less is known about the primary infection of HHV-6A. Both viruses are neurotropic and have capacity to establish lifelong latency in cells of the central nervous system, with potential to reactivate and cause complications later in life. HHV-6A infection has been associated with an increased risk of multiple sclerosis (MS), whereas HHV-6B is indicated to be involved in pathogenesis of epilepsy. These two associations show how neurological diseases might be caused by viral infections, but as suggested here, through completely different molecular mechanisms, in an autoimmune disease, such as MS, by triggering an overreaction of the immune system and in epilepsy by hampering internal cellular functions when the immune system fails to eliminate the virus. Understanding the viral mechanisms of primary infection and reactivation and their spectrum of associated symptoms will aid our ability to diagnose, treat and prevent these severe and chronic diseases. This review explores the role of HHV-6A and HHV-6B specifically in MS and epilepsy, the evidence to date and the future directions of this field.

1 | INTRODUCTION

Human herpesviruses (HHV) 6A and 6B (HHV-6B) are large, enveloped double-stranded DNA betaherpesviruses. They are considered as ubiquitous in the population but have been notoriously hard to distinguish from each other with

serological assays, and therefore, the precise view of the geographical and age distributions of these two viruses is yet to be determined. Here, we will refer to them as HHV-6 when citing studies where they have not been separated, and as such, they occur in over 90% of the adult population and establish itself early in life.¹ Primary infection with

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. *Scandinavian Journal of Immunology* published by John Wiley & Sons Ltd on behalf of The Scandinavian Foundation for Immunology

HHV-6B generally occurs in infancy, when the protective maternal antibodies wane, and presents with a self-limiting undifferentiated febrile illness and in a portion with roseola infantum.²⁻⁴ Although there are less epidemiological data about HHV-6A, it seems to be more common in Africa and to have an asymptomatic primary infection.⁵ Similar to other herpesviruses, HHV-6 viruses are extremely efficient at evading the immune system, and as a result, they can establish lifelong latency in the host in wide range of cell types including cells of the central nervous system (CNS). Viral reactivation of HHV-6 can occur, particularly in immunosuppressed hosts. This can lead to a number of diseases including acute encephalitis, but has also been implicated in the pathogenesis of chronic neurological diseases such as multiple sclerosis (MS) and epilepsy.^{6,7}

There are several ways that viruses are implicated in pathogenesis of chronic brain diseases. In animal models, the same virus (Theiler's murine encephalomyelitis virus) can cause either MS-like disease or epilepsy depending on which mouse strain (SJL/J or C57BL/6J) is infected intrathecally.⁸ This indicates the importance of host genetics in regulating immunity and pathogenesis. HHV-6B has been detected in brain tissue surgically removed from patients with epilepsy.^{7,9,10} Persons with MS have an increased serological response to a selected antigen from HHV-6A, but not from HHV-6B, and this increase was also seen in serum collected before the MS diagnosis and thus it confers a risk factor for MS.¹¹ In addition, HHV-6A and HHV-6B are implicated in a number of other neurological diseases which commonly present with seizures or encephalitis, including HHV-6 post-transplant acute limbic encephalitis (HHV-6 PALE), Rasmussen encephalitis and febrile seizures in children.¹² It is important to consider these complications of HHV-6 infection in patients treated with immunomodulatory drugs due to their associated risk of treatment-related opportunistic infections.¹³ This review will, however, only explore the role of HHV-6A and HHV-6B specifically in epilepsy and MS, the evidence to date and the future directions of this field.

2 | MAIN TEXT

2.1 | Human herpesvirus 6A and 6B structures and immune system interactions

There are nine herpesviruses known to be human pathogens. HHV-6A and HHV-6B are two distinct species belonging to the β -herpesviruses subfamily in the roseola virus genus. Despite sharing 90% of their nucleotide sequence, the two virus isolates demonstrate both genetic and phenotypic variation.^{14,15} They were initially classified as separate strains of the same virus, but were in 2012 concluded to be two distinct species.¹⁶ Through epigenetic modifications and histone modification, the virus can integrate itself into the telomeric part of the chromosomes of infected cells.^{17,18} This includes the germ cells, from where it can be inherited in a mendelian fashion, resulting in 1% of the human population having HHV-6A or HHV-6B genome integrated into the genome of all cells in the body.¹⁹ One defined receptor for HHV-6 infection is the complement inhibitor CD46.²⁰ It is a cell surface protein expressed on all nucleated cells and thus gives the viruses a very large range of possible host cells, including CNS cells such as oligodendrocytes, astrocytes and glial cells.²¹ This receptor is considered to be more exploited by HHV-6A, whereas HHV-6B uses CD134, a primarily T cell surface protein, as a primary receptor. HHV-6B might then have a more restricted tropism that would not include the brain cells.²² However, large and enveloped viruses such as human herpesviruses can incorporate cellular proteins from the host cell into its envelope, including their own receptor.²³ Therefore, for every new cell type the virus infects and replicates from it will change its protein content and acquire a new set of potential receptors and thereby possibly expand its tropism (Figure 1). This mechanism of incorporation of in particular complement inhibitory proteins could be a general immune evasion strategy of viruses. Several viruses are known to have the complement inhibitory proteins CD46, CD55 and CD59 incorporated in their envelope, which will protect them against complement lysis.²⁴⁻²⁶ Incorporation of host cells proteins and lipids into larger enveloped viral particles is a well-known phenomenon by virologists, but deserves to be

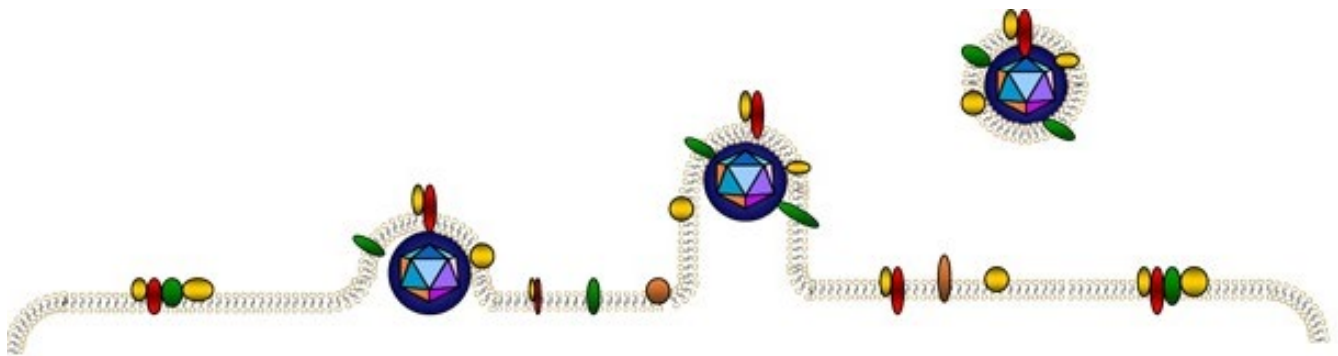


FIGURE 1 The concept of how larger enveloped viruses form their membrane by budding out of the host cell membrane and thus bringing the proteins and lipids from the host cell integrated into the viral particle

explored further by immunologists to determine which immunopathological events might be explained by this mechanism.

The proteins that are incorporated following infection of brain cells have not yet been investigated, and we do not know if this could lead to autoimmunity. In autoimmunity, molecular mimicry is a widely accepted hypothesis, postulating that expression of microbe-encoded genes generates protein and peptide epitopes which are sufficiently similar to mammalian host-encoded proteins to evoke cross-reactive activation of the immune system.²⁷ In contrast to the incorporation theory, the mimicking sequence triggering autoreactive T and B cells can be identified on nucleic acid level, by comparing the host genome to the viral genome. Incorporated antigens, however, can only be identified using proteomic analyses of viral particles cultivated in the host cell of interest. Since viral incorporation adds a new dimension to the molecular mimicry hypothesis, it is intriguing to explore how the immune system will handle viral particles with different cellular protein and lipid components and if cell-specific autoimmunity is triggered dependent on which cell type the virus is propagated in.

2.2 | The role of human herpesvirus 6A in multiple sclerosis

Many autoimmune diseases have been associated with different herpesviruses (reviewed in Ref. (28)). MS is a chronic, inflammatory, demyelinating disease of the central nervous system. The aetiology of MS is unknown, but both genes and environmental risk factors have been identified.²⁹ Several different viruses have been suggested to be associated with MS, but what makes HHV-6 an attractive candidate for MS aetiology is that it has been found to be present in the oligodendrocytes of MS plaques.^{30,31}

Several studies have investigated the specific association between HHV-6 and MS.^{6,32,33} There are contradictory results, but a role for HHV-6A has been proposed³⁴⁻³⁶ and an association with circulating IgM levels with MS has been replicated.^{32,37} The difficulty to distinguish between HHV-6A and HHV-6B with serological methods might be one explanation for the discrepancies of these studies. However, in a collaborative project investigating the serological response of over 8500 persons with MS and around 7000 healthy controls, as well as in samples taken before disease onset, we could recently support an association between seropositivity against the HHV-6A antigen IE1A (OR = 1.55, $P = 9 \times 10^{-22}$) and increased risk of future MS (OR = 2.22, $P = 2 \times 10^{-5}$), but not for the corresponding HHV-6B antigen IE1B.¹¹

Since as described, HHV-6A is a large enveloped virus and can incorporate host cell proteins into its envelope (Figure 1), it would be an attractive candidate for the alternative mechanism of incorporation, worth exploring as an aetiological factor of autoimmunity in MS.^{23,38} For MS, viral particles propagated in

the myelin-producing oligodendrocytes might contain myelin proteins/lipids, but this has not been characterized yet. There are, however, several interesting examples from other enveloped viruses, indicating that this is a general phenomenon, such as human Immunodeficiency virus (HIV) which incorporates several proteins,^{39,40} and vesicular stomatitis virus (VSV) which incorporates myelin basic protein (MBP) when cultivated in MBP-expressing cells.⁴¹ When encountered by the immune system, antigen-presenting cells (APCs) that have phagocytosed these viruses would present a wide range of peptides, derived from both viral proteins and incorporated myelin proteins from the oligodendrocyte host cell. Hence, specific B and T cell response against antigens from both the virus and the host cell might be activated. In addition, lipid-specific B cells might become activated against the lipids of the host cell when these are taken up as part of the viral envelope by the B cell. One other virus with known tropism for oligodendrocytes, the John Cunningham virus (JCV), is a less likely candidate for autoimmunity since it is non-enveloped and causes rapid viral-mediated fatal disease of the host. Therefore, this pathology would be completely different from the incorporation hypothesis for autoimmunity, as we suggest is also the case for the role of HHV-6B in epilepsy.

2.3 | The role of human herpesvirus 6B in epilepsy

Epilepsy is a common disease characterized by the uncontrolled overexcitatory activity of neurons, which results in seizures and convulsions. There are several different causes of the disease, but in many cases, the aetiology is unknown. To date, there are no cures for epilepsy, but the seizures are controlled by anti-epileptic drugs. In severe medically refractory epilepsy, surgery is used to remove the part of the brain from where the seizures originate.

In surgically excised hippocampal tissue from patients with mesial temporal lobe epilepsy (MTLE), we and others have found high HHV-6B viral DNA load,^{7,10} indicating an association between the virus and epilepsy and indicating that HHV-6B infection can be found in the brain despite the lack of expression of CD134 (according to the protein atlas).⁴² In the epileptic tissue, HHV-6B viral proteins were detected in astrocytes, indicating at least partial activity of the virus through gene expression.^{7,43} These cells are important for the clearing of neurotransmitters to terminate neuron signalling, and the presence of viral proteins, even without complete viral replication, might hamper this function.

Using a nested PCR technique, HHV-6 has been recorded in 24%-43% of brain biopsies collected from healthy individuals.⁴⁴⁻⁴⁶ However, even if viral DNA is present, viral proteins do not always seem to be expressed.⁴⁶ In vitro studies have shown that human glial precursor cells can be infected by both HHV-6A and HHV-6B,⁴⁷ while only HHV-6A establishes a productive infection in astrocyte cultures.^{48,49} HHV-6B does

not replicate in astrocytes *in vitro*, but low levels of DNA can be detected in the cells for >6 cell passages,^{49,50} suggesting that HHV-6B might become latent in astrocytes.

One hypothesis is that HHV-6B establishes itself as an infection in the brain during childhood in glial precursor cells, possibly only as incompletely replicating, but enough to cause modifications of the host cells. Alternatively, latency could be followed by recurrent incomplete reactivations, enough to hamper the function of the astrocytes to a degree that affects the clearance of neurotransmitters, thus causing epileptic symptoms.

It has been suggested that latency of herpesviruses is regulated by epigenetic mechanisms. Primarily, upon virus entry of a cell, the viral genome is folded around histones and the 'tails' are modified to repress or enhance gene expression (reviewed in Ref. (51)). Viral DNA also becomes methylated, which is a marker of transcriptional repression and possibly an effort of the host cell to control the virus. Quiescent cytomegalovirus (CMV), a herpesvirus closely related to HHV-6, reactivates from latency upon de-methylation of the viral DNA and by de-acetylation of histone tails.⁵² We have discovered that HHV-6B affects the host cell subtelomere methylation during active infection, which correlates with virus integration into the host cell telomeres, indicating that the virus uses the host epigenetic machinery to modify the epigenetic landscape for its own survival.⁵³ In recent years, it has been suggested that epigenetic modulations might play a role in epilepsy,⁵⁴ but these studies did not investigate the presence of the virus in the tissue.

Our preliminary results indicate that HHV-6B affects the MAPK kinase signalling pathway, both *in vivo* of brain tissue from epilepsy brain surgery and *in vitro* in T cell lines. This pathway has been shown to be affected in status epilepticus⁵⁵ and that some proteins in this pathway are activated in areas with astrogliosis in epileptic hippocampal tissue.⁵⁶ More specifically, activation of the MAPK cascade can trigger local energy deficit⁵⁷ and cytoskeleton reorganization during viral infection.⁵⁸ It has been shown that MAP2K4/MKK4 is important for induced vacuolization of glioblastoma cells,⁵⁹ which might be associated with the two classical features of HHV-6B infection that are change in cell morphology and vacuolization of cells. However, the molecular mechanisms underlying these morphological changes if they are important for vesicle transportation have not as yet been investigated. Thus, HHV-6B might contribute to the pathogenesis in epilepsy by interfering with the vesicular transport system through the MAPK pathway, leading to disturbed glutamate uptake by infected astrocytes. Both viral-induced epigenetic modification and how HHV-6B modifies host cell functions deserve further investigations, and possible mechanisms of how this might lead to epileptic symptoms are of interest to explore. The challenge for immunologist here is to understand how the viral infection can establish itself in the brain

without any apparent detection and elimination efforts by the immune system.

3 | SIGNIFICANCE AND FUTURE PERSPECTIVE

We are only at the start of understanding of the significance of HHV-6A and HHV-6B in MS and epilepsy and the contrasting ways they may cause pathology. Future studies have the potential to contribute in enhancing the basic knowledge about these viruses in different cell types, improving the sensitivity, specificity and throughput of diagnostic tests, as well as finding suitable treatments, interventions and potential prophylaxis.

Basic scientific knowledge about how HHV-6A and HHV-6B efficiently evade the immune system and, similar to other herpesviruses, establish latency with potential to reactivate later in life needs further investigations. By increasing our understanding of the molecular and cellular mechanisms driving these processes, we not only learn more about specific neurological diseases, but also about the immune system regulations and viral infections in general and the counteracting immune evasion strategies. To address whether incorporation of host cell proteins and lipids in the virion might be an alternative mechanism to explain the specificity of autoimmunity in general, the virus needs to be cultivated in the target cell of the disease. Even though incorporation is not new in the virology field, we are only in the beginning of understanding how the immune system handles these host cell-specific viral particles. For MS, characterizing a significant host cell-specific protein signature of HHV-6A from human oligodendrocytes should be prioritized. At the other end of the spectrum, the ability of HHV-6B to hamper the function of human astrocytes, without evoking extensive immune reactions, should be studied in more detail including epigenetic modifications; chromosomal integrations; and potential reactivation strategies targeting these viral-induced modifications. With recent advancements making it possible to cultivate human CNS cells *in vitro* as organoids from inducible pluripotent stem cells, single-cell analysis and high-throughput 'omics' technology platforms, the feasibility of these types of experiments has increased. An alternative is to investigate this mechanism in the marmosets, an animal model that develops MS-like symptoms when infected with HHV-6A but not with HHV-6B.⁶⁰ Further explorations of other viruses with similar characteristics and tropisms as HHV-6A and HHV-6B, which might also stimulate similar autoimmune responses or viral-mediated dysfunctions, are warranted.

Diagnostic testing of HHV-6A and HHV-6B is centred around detection of DNA with PCR or antibodies with serology. The primary limitation of identifying an active infection by detecting extracellular DNA with PCR test is

that it will only be positive if your sample is taken during a viremia, which typically only lasts a few days after infection, and thus, the time window to detect the virus is very narrow. Although this method is useful for triaging patients with severe acute infections in the hospital, it will be less informative as a potential diagnostic tool for chronic diseases such as MS and epilepsy. Here, one would have to apply a combination of methods detecting HHV-6A and HHV-6B DNA and proteins in cerebrospinal fluid compared to sera in conjunction with specific serological tests of IgM and IgG, as has been done in studies of febrile seizures and epilepsy.⁶¹ Clearly, since almost everyone is infected, it is not enough to detect the virus or immune responses to it, but the additional events that might lead to CNS pathologies need to be characterized and used as diagnostic tools. This is particularly true for epilepsy, where no viral DNA was detected in blood, although high copy numbers were detected in hippocampus of the same individuals.⁷ Similarly, no viral DNA or pleocytosis was detected in CSF in the children with febrile seizures associated with HHV-6B.⁶¹ Thus, to be able to identify cases where HHV-6B is present in astrocytes and is causing pathology, novel inductions of biomarkers or downregulation of essential housekeeping genes might be alternatives worth exploring.

Discoveries of novel biomarkers in CNS cells from in vitro cultures could potentially enable identification of these viral traces in clinical samples. The ability of the viruses to integrate their genome early in acute infection of neural cells through epigenetically regulated mechanisms, affecting gene expression and inducing dysregulation of neural host cell functions, should be explored further. In the case of the incorporation hypothesis for autoimmunity, a combination of serological specificities both against the virus and the potentially incorporated host cell proteins from human oligodendrocytes might reveal if such events happen in vivo and are of clinical relevance. These could be used to better stratify patient groups, and if these viruses have any implications for the pathogenesis of CNS diseases, diagnostic tests for characterizing subgroups of epilepsy and MS can be developed. These would enable identification of when the viral infection should be treated.

Development of therapeutic interventions for HHV-6A and HHV-6B infection, reactivation and complications is centred around antiviral therapy, where a limited set of drugs is available. Patients with complicated HHV-6 infection are treated with antiviral drugs such as ganciclovir despite being toxic and in some cases ineffective against HHV-6 infection.⁶² Upcoming novel alternatives are for example the recent advances in immunotherapies including viral-specific adoptive T cell immunotherapy and HHV-6-specific neutralizing antibodies that have been successful in early trials.^{63,64} Furthermore, strategies using CRISPR-Cas9 to target viral genomes are also in progress.⁶⁵ This will be imperative for

patients with MS or epilepsy to remove the virus from the specific target cells, if found to be contributing to disease activity and progression. Thus, a better understanding of specific pathogenic mechanisms will enable development of new treatments strategies directed against the pathways dysregulated by the virus, epigenetic modifications or the integrated DNA of the virus. Potential future prophylaxis is currently developed for HHV-6 and other viruses, using T cell infusions.⁶⁶ However, given the ubiquitous nature of these viruses, the possible negative implications of eradication of HHV-6A and HHV-6B must be considered when deciding on the use of prophylactics. It has been suggested that herpesviruses might form a symbiotic relationship with the host with their systemic activation of macrophages and induction of the interferon system, protecting the host against lethal bacterial infections.⁶⁷ Whether this protection is true for humans and for how long it might last remains to be determined, but it indicates that removing highly adapted viral infections from the human population might have unforeseen consequences.

ACKNOWLEDGMENTS

We would like to acknowledge the previous research group members who contributed significantly to the HHV-6A and HHV-6B work: Dr Elin Engdahl, Dr Rasmus Gustafsson and Dr Jenny Ahlqvist. We would also like to thank Dr Steven Jacobson (Viral Immunology Section of NINDS, NIH), Professor Louis Flamand, Professor Dharam Ablashi and Kristin Loomis for all of the support and valuable discussions from the HHV-6&7 Foundation.

CONFLICT OF INTEREST


The authors have no conflict of interest to report.

AUTHOR CONTRIBUTIONS

AFH drafted the manuscript. ND and NK reviewed, edited and approved the final version.

ORCID

Nicky Dunn  <https://orcid.org/0000-0001-9294-6124>

Anna Fogdell-Hahn  <https://orcid.org/0000-0002-0311-9184>

REFERENCES

1. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev.* 2015;28(2):313-335.
2. Hall CB, Caserta MT, Schnabel KC, et al. Characteristics and acquisition of human herpesvirus (HHV) 7 infections in relation to infection with HHV-6. *J Infect Dis.* 2006;193(8):1063-1069.
3. Dewhurst S, McIntyre K, Schnabel K, Hall CB. Human herpesvirus 6 (HHV-6) variant B accounts for the majority of symptomatic primary HHV-6 infections in a population of U.S. infants. *J Clin Microbiol.* 1993;31(2):416-418.

4. Braun DK, Dominguez G, Pellett PE. Human herpesvirus 6. *Clin Microbiol Rev.* 1997;10(3):521-567.
5. Bates M, Monze M, Bima H, et al. Predominant human herpesvirus 6 variant A infant infections in an HIV-1 endemic region of Sub-Saharan Africa. *J Med Virol.* 2009;81(5):779-789.
6. Challoner PB, Smith KT, Parker JD, et al. Plaque-associated expression of human herpesvirus 6 in multiple sclerosis. *Proc Natl Acad Sci USA.* 1995;92(16):7440-7444.
7. Donati D, Akhyani N, Fogdell-Hahn A, et al. Detection of human herpesvirus-6 in mesial temporal lobe epilepsy surgical brain resections. *Neurology.* 2003;61(10):1405-1411.
8. DePaula-Silva AB, Hanak TJ, Libbey JE, Fujinami RS. Theiler's murine encephalomyelitis virus infection of SJL/J and C57BL/6J mice: Models for multiple sclerosis and epilepsy. *J Neuroimmunol.* 2017;308:30-42.
9. Wipfler P, Dunn N, Beiki O, Trinka E, Fogdell-Hahn A. The viral hypothesis of mesial temporal lobe epilepsy—Is human herpes virus-6 the missing link? A systematic review and meta-analysis. *Seizure.* 2018;54:33-40.
10. Li JM, Lei D, Peng F, et al. Detection of human herpes virus 6B in patients with mesial temporal lobe epilepsy in West China and the possible association with elevated NF-kappaB expression. *Epilepsy Res.* 2011;94(1-2):1-9.
11. Engdahl E, Gustafsson R, Huang J, et al. Increased serological response against human herpesvirus 6A is associated with risk for multiple sclerosis. *Front Immunol.* 2019;10:2715.
12. Eliassen E, Hemond CC, Santoro JD. HHV-6-associated neurological disease in children: epidemiologic, clinical, diagnostic, and treatment considerations. *Pediatr Neurol.* 2020;105:10-20.
13. Baumer T, Fry C, Luppe S, Gunawardena H, Sieradzan K. Human herpes virus-6 encephalitis causing severe anterograde amnesia associated with rituximab, azathioprine and prednisolone combination therapy for dermatomyositis. *J Neurovirol.* 2017;23(3):508-510.
14. Dominguez G, Dambaugh TR, Stamey FR, Dewhurst S, Inoue N, Pellett PE. Human herpesvirus 6B genome sequence: coding content and comparison with human herpesvirus 6A. *J Virol.* 1999;73(10):8040-8052.
15. Greninger AL, Knudsen GM, Roychoudhury P, et al. Comparative genomic, transcriptomic, and proteomic reannotation of human herpesvirus 6. *BMC Genom.* 2018;19(1):204.
16. Adams MJ, Carstens EB. Ratification vote on taxonomic proposals to the International Committee on Taxonomy of Viruses (2012). *Arch Virol.* 2012;157(7):1411-1422.
17. Engdahl E, Dunn N, Niehusmann P, et al. Human herpesvirus 6B induces hypomethylation on chromosome 17p13.3, correlating with increased gene expression and virus integration. *J Virol.* 2017;91(11).
18. Saviola AJ, Zimmermann C, Mariani M, et al. Chromatin profiles of chromosomally integrated human herpesvirus-6A. *Front Microbiol.* 2019;10:1408.
19. Flamand L. Chromosomal integration by human herpesviruses 6A and 6B. *Adv Exp Med Biol.* 2018;1045:209-226.
20. Santoro F, Kennedy PE, Locatelli G, Malnati MS, Berger EA, Lusso P. CD46 is a cellular receptor for human herpesvirus 6. *Cell.* 1999;99(7):817-827.
21. Cassiani-Ingoni R, Greenstone HL, Donati D, et al. CD46 on glial cells can function as a receptor for viral glycoprotein-mediated cell-cell fusion. *Glia.* 2005;52(3):252-258.
22. Tang H, Serada S, Kawabata A, et al. CD134 is a cellular receptor specific for human herpesvirus-6B entry. *Proc Natl Acad Sci USA.* 2013;110(22):9096-9099.
23. Hammarstedt M, Ahlqvist J, Jacobson S, Garoff H, Fogdell-Hahn A. Purification of infectious human herpesvirus 6A virions and association of host cell proteins. *Virol J.* 2007;4:101.
24. Montefiori DC, Cornell RJ, Zhou JY, Zhou JT, Hirsch VM, Johnson PR. Complement control proteins, CD46, CD55, and CD59, as common surface constituents of human and simian immunodeficiency viruses and possible targets for vaccine protection. *Virology.* 1994;205(1):82-92.
25. Spiller OB, Hanna SM, Devine DV, Tufaro F. Neutralization of cytomegalovirus virions: the role of complement. *J Infect Dis.* 1997;176(2):339-347.
26. Vanderplasschen A, Mathew E, Hollinshead M, Sim RB, Smith GL. Extracellular enveloped vaccinia virus is resistant to complement because of incorporation of host complement control proteins into its envelope. *Proc Natl Acad Sci USA.* 1998;95(13):7544-7549.
27. Wucherpfennig KW, Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. *Cell.* 1995;80(5):695-705.
28. Posnett DN. Herpesviruses and autoimmunity. *Curr Opin Investig Drugs.* 2008;9(5):505-514.
29. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat Rev Neurol.* 2017;13(1):25-36.
30. Blumberg BM, Mock DJ, Powers JM, et al. The HHV6 paradox: ubiquitous commensal or insidious pathogen? A two-step in situ PCR approach. *J Clin Virol.* 2000;16(3):159-178.
31. Cermelli C, Berti R, Soldan S, et al. High frequency of human herpesvirus 6 DNA in multiple sclerosis plaques isolated by laser microdissection. *J Infect Dis.* 2003;187(9):1377-1387.
32. Soldan SS, Berti R, Salem N, et al. Association of human herpes virus 6 (HHV-6) with multiple sclerosis: increased IgM response to HHV-6 early antigen and detection of serum HHV-6 DNA [see comments]. *Nat Med.* 1997;3(12):1394-1397.
33. Álvarez-Lafuente R, De las Heras V, Bartolomé M, Picazo JJ, Arroyo R. Relapsing-remitting multiple sclerosis and human herpesvirus 6 active infection. *Arch Neurol.* 2004;61(10):1523-1527.
34. Virtanen JO, Färkkilä M, Multanen J, et al. Evidence for human herpesvirus 6 variant A antibodies in multiple sclerosis: diagnostic and therapeutic implications. *J Neurovirol.* 2007;13(4):347-352.
35. Soldan SS, Leist TP, Juhng KN, McFarland HF, Jacobson S. Increased lymphoproliferative response to human herpesvirus type 6A variant in multiple sclerosis patients. *Ann Neurol.* 2000;47(3):306-313.
36. Friedman JE, Lyons MJ, Cu G, et al. The association of the human herpesvirus-6 and MS. *Mult Scler.* 1999;5(5):355-362.
37. Ortega-Madueño I, Garcia-Montojo M, Dominguez-Mozo MI, et al. Anti-human herpesvirus 6A/B IgG correlates with relapses and progression in multiple sclerosis. *PLoS One.* 2014;9(8):e104836.
38. Soderberg Naucner CS, Larsson S, Moller E. A novel mechanism for virus-induced autoimmunity in humans. *Immunol Rev.* 1996;152(1):175-192. <https://doi.org/10.1111/j.1600-065X.1996.tb00916.x>
39. Arthur L, Bess J, Sowder R, et al. Cellular proteins bound to immunodeficiency viruses: implications for pathogenesis and vaccines. *Science.* 1992;258(5090):1935-1938.

40. Ott DE. Cellular proteins in HIV virions. *Rev Med Virol.* 1997;7(3):167-180.
41. Lodish HF, Porter M. Specific incorporation of host cell surface proteins into budding vesicular stomatitis virus particles. *Cell.* 1980;19(1):161-169.
42. Uhlen M, Oksvold P, Fegerberg L, et al. Towards a knowledge-based Human Protein Atlas. *Nat Biotechnol.* 2010;28:1248-1250. <https://doi.org/10.1038/nbt1210-1248>
43. Fotheringham J, Donati D, Akhyani N, et al. Association of human herpesvirus-6B with mesial temporal lobe epilepsy. *PLoS Med.* 2007;4(5):e180.
44. Chan PK, Ng HK, Hui M, Cheng AF. Prevalence and distribution of human herpesvirus 6 variants A and B in adult human brain. *J Med Virol.* 2001;64(1):42-46.
45. Chan PKS, Ng H-K, Hui M, et al. Presence of human herpesviruses 6, 7, and 8 DNA sequences in normal brain tissue. *J Med Virol.* 1999;59(4):491-495.
46. Cuomo L, Trivedi P, Cardillo MR, et al. Human herpesvirus 6 infection in neoplastic and normal brain tissue. *J Med Virol.* 2001;63(1):45-51.
47. Dietrich J, Blumberg BM, Roshal M, et al. Infection with an endemic human herpesvirus disrupts critical glial precursor cell properties. *J Neurosci.* 2004;24(20):4875-4883.
48. Ahlqvist J, Donati D, Martinelli E, et al. Complete replication cycle and acquisition of tegument in nucleus of human herpesvirus 6A in astrocytes and in T-cells. *J Med Virol.* 2006;78(12):1542-1553.
49. Donati D, Martinelli E, Cassiani-Ingoni R, et al. Variant-specific tropism of human herpesvirus 6 in human astrocytes. *J Virol.* 2005;79(15):9439-9448.
50. Yoshikawa T, Asano Y, Akimoto S, et al. Latent infection of human herpesvirus 6 in astrocytoma cell line and alteration of cytokine synthesis. *J Med Virol.* 2002;66(4):497-505.
51. Knipe DM, Cliffe A. Chromatin control of herpes simplex virus lytic and latent infection. *Nat Rev Microbiol.* 2008;6(3):211-221.
52. Choi KH, Basma H, Singh J, Cheng PW. Activation of CMV promoter-controlled glycosyltransferase and beta-galactosidase glyco-genes by butyrate, trichostatin A, and 5-aza-2'-deoxycytidine. *Glycoconj J.* 2005;22(1-2):63-69.
53. Engdahl E, Dunn N, Niehusmann P, et al. Human herpesvirus 6B induces hypomethylation on chromosome 17p13.3 correlating with increased gene expression and virus integration. *J Virol.* 2017;91.
54. Kobow K, Jeske I, Hildebrandt M, et al. Increased reelin promoter methylation is associated with granule cell dispersion in human temporal lobe epilepsy. *J Neuropathol Exp Neurol.* 2009;68(4):356-364.
55. Hansen KF, Sakamoto K, Pelz C, Impey S, Obrietan K. Profiling status epilepticus-induced changes in hippocampal RNA expression using high-throughput RNA sequencing. *Sci Rep.* 2014;4:6930.
56. Mandell JW, Vandenberg SR. ERK/MAP kinase is chronically activated in human reactive astrocytes. *NeuroReport.* 1999;10(17):3567-3572.
57. Yang J, Wu Z, Renier N, et al. Pathological axonal death through a MAPK cascade that triggers a local energy deficit. *Cell.* 2015;160(1-2):161-176.
58. Pereira AC, Leite FG, Brasil BS, et al. A vaccinia virus-driven interplay between the MKK4/7-JNK1/2 pathway and cytoskeleton reorganization. *J Virol.* 2012;86(1):172-184.
59. Kitambi SS, Toledo EM, Usoskin D, et al. Vulnerability of glioblastoma cells to catastrophic vacuolization and death induced by a small molecule. *Cell.* 2014;157(2):313-328.
60. Leibovitch E, Wohler JE, Macri SM, et al. Novel marmoset (*Callithrix jacchus*) model of human Herpesvirus 6A and 6B infections: immunologic, virologic and radiologic characterization. *PLoS Pathog.* 2013;9(1):e1003138.
61. Epstein LG, Shinnar S, Hesdorffer DC, et al. Human herpesvirus 6 and 7 in febrile status epilepticus: the FEBSTAT study. *Epilepsia.* 2012;53(9):1481-1488.
62. Zerr DM, Gupta D, Huang ML, Carter R, Corey L. Effect of antivirals on human herpesvirus 6 replication in hematopoietic stem cell transplant recipients. *Clin Infect Dis.* 2002;34(3):309-317.
63. Gerdemann U, Keukens L, Keirnan JM, et al. Immunotherapeutic strategies to prevent and treat human herpesvirus 6 reactivation after allogeneic stem cell transplantation. *Blood.* 2013;121(1):207-218.
64. Wang B, Nishimura M, Maekawa Y, Kotari T, Okuno T, Mori Y. Humanization of murine neutralizing antibodies against human herpesvirus 6B. *J Virol.* 2019;93(10).
65. Lee C. CRISPR/Cas9-based antiviral strategy: current status and the potential challenge. *Molecules.* 2019;24(7).
66. Papadopoulou A, Gerdemann U, Katari UL, et al. Activity of broad-spectrum T cells as treatment for AdV, EBV, CMV, BKV, and HHV6 infections after HSCT. *Sci Transl Med.* 2014;6(242):242ra83.
67. Barton ES, White DW, Cathelyn JS, et al. Herpesvirus latency confers symbiotic protection from bacterial infection. *Nature.* 2007;447(7142):326-329.

How to cite this article: Dunn N, Kharlamova N, Fogdell-Hahn A. The role of herpesvirus 6A and 6B in multiple sclerosis and epilepsy. *Scand J Immunol.* 2020;92:e12984. <https://doi.org/10.1111/sji.12984>