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Classification of HHV-6A and HHV-6B as distinct viruses

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Abstract

Shortly after the discovery of human herpesvirus 6 (HHV-6), two distinct variants, HHV-6A and HHV-6B, were identified. In 2012, the International Committee on Taxonomy of Viruses (ICTV) classified HHV-6A and HHV-6B as separate viruses. This review outlines several of the documented epidemiological, biological, and immunological distinctions between HHV-6A and HHV-6B, which support the ICTV classification. The utilization of virus-specific clinical and laboratory assays for distinguishing HHV-6A and HHV-6B is now required for further classification. For clarity in biological and clinical distinctions between HHV-6A and HHV-6B, scientists and physicians are herein urged, where possible, to differentiate carefully between HHV-6A and HHV-6B in all future publications.

Introduction and classification history

In 1986, a new virus was isolated in the USA from patients with AIDS as well as lymphoproliferative disorders [111]. Initially designated “human B-lymphotropic virus (HBLV)”, the virus was renamed human herpesvirus 6 (HHV-6) (GS strain), following herpesvirus nomenclature guidelines, soon thereafter [2]. In 1987 and 1988, independent isolates were obtained from AIDS patients in Africa, designated U1102 (from Uganda) [50] and Z29 (from Zaire) [80, 124]. As other strains were isolated from various geographic regions and clinical settings, it became gradually apparent that all HHV-6 isolates could be included in one of two well-defined groups, differing in their molecular, epidemiological and biological properties [4, 16, 71, 113, 129]. The two groups showed different *in vitro* tropism for selected T cell lines, specific immunological reactivity with monoclonal antibodies, distinct patterns of restriction endonuclease sites, and specific and conserved interstrain variations in their DNA sequences [68, 69, 71].

In the early 1990s, the scientific community debated whether the two groups simply reflected a normal population heterogeneity within a single virus species [113], and in 1992 a first consensus was reached to designate such groups as two variants of the same species:

HHV-6A and HHV-6B [1]. This decision was based on two main factors: (i) the interspecies divergence of nucleic acids was remarkably low and (ii) there was limited knowledge of differential epidemiology and pathogenic potential [1]. However, as new evidence continued to accrue, several authors began to suggest that the two variants be recognized as distinct viruses [22, 24, 32, 45].

Genomic sequencing has now confirmed distinctions between HHV-6A and HHV-6B and relationships to the herpesvirus family overall. The genomes of the these two viruses are co-linear and share an overall identity of 90 %, but divergence of specific sequences [e.g., the immediate-early (IE) region] is higher than 30 %, some from splicing differences [47, 58, 67], and there are clear functional differences in the IE1 gene of HHV-6A and HHV-6B [59, 70]. Remarkably, even though the IE1 gene differs substantially between HHV-6A and HHV-6B, this region is highly conserved (>95 %) within clinical and laboratory isolates of each virus [116]. Analysis of different viral strains shows that even highly conserved sequences with homology higher than 95 %, such as gH, gB and U94, as well as divergent genes such as gN, gO, and U83 chemokine, are characterized by specific amino acid signatures, which permit distinctions between the two viruses [5, 56, 107]. Furthermore, several reports have shown that the splicing pattern and temporal regulation of transcription of selected genes are different [47, 67, 92, 102, 103]. So far, these distinctions and the absence of evidence of intervariant recombination in common circulating viruses suggest that the two groups do occupy different ecological niches *in vivo* [24].

An *Ad Hoc Committee on HHV-6A & HHV-6B Genomic Divergence* was formed in 2009 to generate an official proposal to recognize HHV-6A and HHV-6B as distinct viruses, which was submitted to the ICTV in 2010. In 2012, the ICTV officially ratified the classification of HHV-6A and HHV-6B as distinct viruses, replacing species *Human herpesvirus 6* with *Human herpesvirus 6A* and *Human herpesvirus 6B* in the genus *Roseolovirus*, subfamily *Betaherpesvirinae*, family *Herpesviridae*, order *Herpesvirales. Human herpesvirus 6A* has been designated as the type species in this genus [6].

The following is a detailed summary of several known distinctions between HHV-6A and HHV-6B, which ultimately led or added support to the classification of these agents as separate and distinct viruses.

Distinct epidemiology and disease associations

1. In the USA, UK and Japan, 97–100 % of primary infections by these two viruses are caused by HHV-6B and occur between the ages of 6 and 12 months [43, 51, 125, 130, 134]. Less is known about the epidemiology of HHV-6A infection. One report has indicated that HHV-6A infection is acquired later in life and that primary infection is typically without clinical symptoms [40]. However, several groups have now documented symptomatic HHV-6A primary infections amongst children from both the USA and Africa [18, 63]. In addition, HHV-6A was found to be the predominant virus associated with viremic infection in a pediatric population of Sub-Saharan Africa [18] and has also been shown to cause roseola and febrile disease in this population. In two separate studies, HHV-6A was detected in blood

DNA from hospitalized febrile HIV+ children from this geographic population [18, 72]. Although this specific correlation awaits further confirmation from other tissue sites and from populations in other regions of Africa, this finding is potentially significant because HHV-6A has been proposed as a potential accelerating factor in HIV infection, as corroborated by the results of *in vivo* studies in macaques [19, 87].

2. HHV-6A and HHV-6B have differential distributions in human tissues. HHV-6B is the dominant virus present in the peripheral blood mononuclear cells (PBMCs) of healthy adults, at least in industrialized countries, and is also the virus that reactivates in a significant majority of both solid organ and stem cell transplant cases in these countries [21, 28, 45, 53, 57, 65, 74, 100, 108, 128], while both HHV-6A and HHV-6B are detected with similar frequency in the plasma of bone marrow transplant patients [97, 114]. HHV-6B is also frequently detected in the GI tract of solid organ transplant patients [76], has been identified in endodontic abscesses [54], and is the virus found in adenoids and tonsils, particularly in children affected by upper airway infections [35]. HHV-6A has been found in 54 % of the lungs of healthy adults [36], although this requires confirmation in other studies and/or regions. Both HHV-6A and HHV-6B have been identified in vitreous fluid samples and implicated in ocular inflammatory diseases [34, 117]. However, it must be noted that these observed differential distribution patterns in human tissues may reflect, at least in part, the differing prevalence of the two viruses in separate geographic regions.

3. While HHV-6A and HHV-6B are both neurotropic, there is evidence suggesting an increased severity of HHV-6A over HHV-6B in cases of clinical neurological disease [21, 37, 40, 62]. In addition, although an overwhelming majority of post-transplant reactivation occurs with HHV-6B [28, 29, 53], HHV-6A DNA and mRNA are found more frequently than HHV-6B in patients with neuroinflammatory diseases such as multiple sclerosis (MS) [9, 14, 48, 115] and rhomboencephalitis [37]. HHV-6A has been found predominantly in the CNS of a subset of patients with MS, and active HHV-6A infection has been detected in blood [8, 9, 11] and in CSF [110] of patients with relapsing/remitting MS [8–10, 14, 20, 110, 115, 131]. Marmosets inoculated with HHV-6A intravenously exhibited neurological symptoms, whereas those inoculated with HHV-6B were asymptomatic [75]. A strain of HHV-6A has also recently been isolated from the fluid specimens from a glioma cyst [30]. Moreover, HHV-6A was identified in 72 % of pediatric glial tumors [38].

4. HHV-6B, but not HHV-6A, has been associated with mesial temporal lobe epilepsy and status epilepticus [52, 77, 126].

5. HHV-6A, but not HHV-6B, has been associated with Hashimoto's thyroiditis [25] as well as syncytial-giant cell hepatitis in liver transplant patients [9, 12, 13, 62, 82, 91, 104–106].

Distinct biological and immunological properties

1. Although both HHV-6A and HHV-6B have been reported to have a strong CD4+T-lymphocyte tropism both *in vitro* and *in vivo* [31, 83, 96, 118], there are some important differences in their ability to infect cytotoxic effector cells [39]. While HHV-6A has been shown to productively infect CD8+ T cells, natural killer (NK) cells and gamma/delta T cells, inducing *de novo* expression of CD4 messenger RNA and protein that is otherwise not expressed in these cell subsets [84–86], HHV-6B can infect these cells very inefficiently, if at all [60, 90].

2. HHV-6B, but not HHV-6A, infects and induces CPE in Molt-3 cells, and HHV-6A, but not HHV-6B, infects and induces CPE in HSB-2 cells [1, 3, 4, 7, 78]. HHV-6A, but not HHV-6B, successfully replicates in human neural stem cells [41] and in human progenitor-derived astrocytes [49, 61]. Although only supporting low levels of infection, human fibroblast cell lines appear more permissive to HHV-6A than HHV-6B *in vitro* but still require copropagation with PBMCs [109]. HHV-6B infection in the astrocytic cell line U251 leads to abortive infection, whereas with HHV-6A, it leads to replication [49, 133]. HHV-6A, but not HHV-6B, can replicate in oligodendrocyte progenitor cells [7, 46, 49].

3. Variation in cellular tropism may be related to the use of alternative cellular receptors by the two viruses. Although both HHV-6A and HHV-6B have been shown to utilize CD46 as a cellular receptor [112, 121], the modality and/or affinity of receptor interaction seem to differ between the two viruses. It has been suggested that HHV-6A (U1102 or GS), but not HHV-6B, can induce CD46-mediated cell-cell fusion without viral replication [93] through a tetrameric complex composed of glycoproteins gH, gL, and gQ1, and gQ2 [94, 122]. However, some groups have reported that HHV-6B is also able to induce cell-cell fusion without viral replication [99].

4. CD134, a member of the TNF receptor superfamily present on activated T lymphocytes, has recently been identified as a receptor molecule for HHV-6B, selectively interacting with the gH/gL/gQ1/gQ2 complex of HHV-6B [123].

5. The HHV-6A and HHV-6B gO gene products have 76.8% amino acid sequence identity, which is much lower than the identity between other glycoproteins. The lower identity suggests that the gH–gL–gO complex may confer at least some of the different biological properties on HHV-6A and HHV-6B that cause them to target different cells [18, 95, 122].

6. Variations in cellular tropism may also be related to the ability to chemoattract distinct cellular populations via specific virus chemokines. Chemokine U83B from HHV-6B is specific for CCR2 and can chemoattract cells for latent or lytic infection that bear this receptor, such as monocytic cells and some T cell subpopulations. In contrast, chemokine U83A from HHV-6A has broader specificity for CCR1, CCR4, CCR5, CCR6 and CCR8, which are present on monocytic/macrophage, dendritic, NK, plus activated and skin-homing T cells [27, 33, 44, 88]. Of note, U83 is also one of the few hypervariable genes that is specific

for HHV-6A and HHV-6B but not shared with the related HHV-7 and therefore encodes key distinctions for these viruses [33, 56].

7. The glycoprotein-encoding genes that encode gQ (U97, 98, 99 and 100) of HHV-6A and HHV-6B share only 72.1% sequence identity [67]. This glycoprotein may therefore have a role in the differential effects of HHV-6A and HHV-6B infections. gQ1, along with gB and gH, contains epitopes recognized by neutralizing antibodies and represents a target for virus-specific neutralizing antibodies [73, 89, 98, 102, 103, 120]. The gH/gL/gQ1/gQ2 complex is an important target for virusneutralizing antibodies [89, 95].

8. HHV-6B, but not HHV-6A, was shown to be resistant to the antiviral effects of interferon-α and –β due to silencing of interferon-stimulated genes [70].

9. Although HHV-6A and HHV-6B stimulate crossreactive T-cell responses because they share more than 88 % sequence homology, it has been reported that at least 7 %of the T-cell clones that are reactive to HHV-6 demonstrate a specific and distinct pattern of proliferation either to HHV-6A or HHV-6B *in vitro* [132].

10. Several monoclonal antibodies are virus-specific. For example, 2E2 (reacting with gp110), 2-D6 (reacting with gp82/105), 13-D6 (reacting with gp82/105) [17], C-5 (reacting with p38/41) [68], p6H8 (reacting with IE-2) [15, 127], and gp110 (reacting with 2E2) [68] are specific for HHV-6A, while OHV-3 (reacting with p98) [17, 79, 119] and C3108-103 (reacting with 101K/U11) [101] are specific for HHV-6B.

11. There are functional differences between cells infected with HHV-6A vs. HHV-6B affecting inflammation [33].

Distinction of HHV-6A vs. HHV-6B in publications

The lack of clear distinction between HHV-6A and HHV-6B in the literature makes it difficult to properly assess epidemiological differences and etiologic associations. In light of the ICTV’s official reclassification, the utilization of virus-specific clinical and laboratory assays for HHV-6A and HHV-6B is especially crucial [23, 26, 64, 66]. However, because HHV-6A can be present at lower copy numbers than HHV-6B, assays that rely strictly on melting point analysis for differentiation may be biased toward the detection of HHV-6B, resulting in further confusion [81]. Moreover, reliance on single SNPs, for example in restriction enzyme assays or using ‘specific’ primers or probes in real-time PCR assays, can be misinterpreted due to strain variation unless an extensive characterization of laboratory-adapted and clinical strains has been performed [26]. Furthermore, serology currently cannot differentiate between HHV-6A and HHV-6B. To avoid this complication, the use of comprehensive virus-specific assays is preferred, combined with confirmation using nucleotide sequencing [18, 26, 42, 55, 57]. In an effort to bring additional clarity to the important biological and clinical distinctions between HHV-6A and HHV-6B, we herein urge scientists and physicians to carefully differentiate, whenever possible, between HHV-6A and HHV-6B in all future publications.

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