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Human herpesvirus-6 strain groups: a nomenclature

Human herpesvirus-6 (HHV-6) was first isolated from individuals with lymphoproliferative disorders (strain GS) [1]. Subsequent isolations of HHV-6 included those from AIDS patients in Uganda (strain U 1102) [2] and Zaire (strain Z 29) [3], and the virus has now been isolated in many laboratories. Accumulating evidence has indicated that HHV-6 isolates form at least two groups, which can be distinguished by differences in molecular and biological properties. The differences between the two groups of HHV-6 have led to a number of informal designations, including "U 1102-like and Z 29-like" [4], "Type I and Type II" [5], "Group A and Group B" [6], and to a proposal [4] that the classification of HHV-6 strains be reconsidered within the formal nomenclature system of the International Committee for Taxonomy of Viruses (ICTV).

The ICTV procedure for naming herpesviruses involves numerical designations for species defined on the basis of "readily assayable and distinctive" differences spanning the entire genome, as well as differences in biology and epidemiology [7]. The need for a consistent, formally agreed nomenclature for each group of HHV-6 isolates was discussed in special sessions at the 16th International Herpesvirus Workshop (Asilomar, July 1991) and at the First International Herpesvirus Symposium in Japan (Osaka, June 1992). Recently, at the 17th International Herpesvirus Workshop (Edinburgh, August 1992) a satellite symposium on HHV-6 was held to specifically address aspects of strain variation and was attended by 65 scientists. We report here a consensus reached by a group of more than 50 scientists present at this symposium and at a subsequent session on nomenclature. Workers not in attendance have been invited to join this consensus.

It was agreed that all HHV-6 isolates examined to date can be assigned to one of two groups on the basis of criteria summarised as follows:

(*i*) All HHV-6 isolates are tropic for CD 4^+ T-lymphocytes, but each group, characterised either by strains GS and U 1102 or by strain Z 29, may preferentially infect different T cell lines [6, 8–10].

(*ii*) Although human sera are reactive with both groups of isolates, each group has a distinct pattern of reactivity with monoclonal antibodies. Four of seven monoclonal antibodies specific for different proteins or glycoproteins of the GS strain reacted with all 31 isolates so far tested, including U 1102 and Z 29, but three recognised epitopes present only in the group which contains GS and U 1102 [4, 6, 8–11].

(*iii*) The two groups can be clearly distinguished by analysis of restriction endonuclease sites. Restriction fragment variations were first reported in studies on strains GS and Z29 [12] and strains U1102 and Z29 [13]. Subsequent work has shown that isolates can be discriminated into two groups on the basis of restriction site polymorphisms [4–6, 11, 14], which extend across the entire genome [4].

(*iv*) Nucleotide sequence analysis also supports the existence of two groups of HHV-6 isolates, but shows that these groups are very closely related to each other and that each contains a degree of heterogeneity, with some regions more variable than others. Sequences (0.2 kb to 2.5 kb) from plasmid clones or polymerase chain reaction amplification products from eight different regions of the genome of laboratory reference strains [15, 16], recent clinical isolates and strains from tissue samples [5, 11, 14] showed that nucleotide sequence identity ranged from 97 to 100% within groups and from 94% to 96% between groups and predicted amino acid sequences from 98% to 100% within groups and 92% to 96% between groups. Comparisons within a group of an 8 kb segment of the genome from GS and U1102 isolates showed 95 to 99.5% nucleotide sequence identity and 95% to 100% amino acid identity [17].

(*v*) All HHV-6 isolates from infants with exanthema subitum and related febrile illness have been Z29-like [4–6, 10, 11], with the exception of two patients from whom both types have been isolated [10]. HHV-6 isolated from immunocompromised adults may belong to either group [1–6, 11, 14], and in one patient both types have been isolated [6]. The prevalence of each group in the population and the relative facility with which viruses from each group can be isolated require further study.

On the question of nomenclature, a consensus was reached that assignment of a new human herpesvirus number to either of the two groups would be premature. In particular, the differential epidemiology of the two groups is unknown, and the significance of the high level of nucleotide sequence similarity between these groups is not yet clear. No pairs of recognized herpesvirus species are known to be as closely related as are the two groups of HHV-6 isolates. The consensus was therefore to identify GS and U1102-like viruses as "HHV-6 variant A" and Z29-like viruses as "HHV-6 variant B", in accordance with a suggestion from the ICTV Herpesvirus Study Group [7] for naming the two closely related groups of HHV-4 (Epstein-Barr virus) strains [18]. It was further agreed that these issues would be discussed at the 18th International Herpesvirus Workshop, to be held in Pittsburgh in August, 1993. Copies of this letter have been circulated to all participants in the symposium held at the 17th International Herpesvirus Workshop and to other interested parties.

References

1. Salahuddin SZ, Ablashi DV, Markham PD, Josephs SF, Sturzenegger S, Kaplan V, Halligan G, Biberfeld P, Wong-Staal F, Kramarsky B, Gallo RC (1986) Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. Science 234: 596–601
2. Downing RG, Sewankambo N, Serwadda D, Honess R, Crawford D, Jarrett R, Griffin BE (1987) Isolation of human lymphotropic herpesviruses from Uganda. Lancet ii: 390
3. Lopez C, Pellett P, Stewart J, Goldsmith C, Sanderlin K, Black J, Warfield D, Feorino P (1988) Characteristics of human herpesvirus-6. J Infect Dis 157: 1271–1279
4. Schirmer EC, Wyatt LS, Yamanishi K, Rodriguez WJ (1991) Differentiation between two distinct classes of viruses now classified as human herpesvirus-6. Proc Natl Acad Sci USA 88: 5922–5926
5. Aubin J-T, Collandre H, Candotti D, Ingrand D, Rouzioux C, Burgard M, Richard S, Huraux JM, Agut H (1991) Several groups among human herpesvirus-6 strains can be distinguished by Southern blotting and polymerase chain reaction. J Clin Microbiol 29: 367–372
6. Ablashi DV, Balachandran N, Josephs SF, Hung CL, Krueger GRF, Kramarksy B, Salahuddin SZ, Gallo RC (1991) Genomic polymorphism, growth properties, and immunologic variations in human herpesvirus-6 isolates. Virology 184: 545–553
7. Roizman B, Desrosiers RC, Fleckenstein B, Lopez C, Minson AC, Studdart MJ (1992) The family *Herpesviridae*: an update. Arch Virol 123: 425–449
8. Wyatt LS, Balachandran N, Frenkel N (1990) Variations in the replication and antigenic properties of human herpesvirus-6 strains. J Infect Dis 162: 852–857
9. Chandran B, Tirawatnapong S, Pfeiffer B, Ablashi DV (1992) Antigenic relationships among human herpesvirus-6 isolates. J Med Virol 37: 247–254
10. Dewhurst S, Chandran B, McIntyre K, Schnabel K, Hall CB (1992) Phenotypic and genetic polymorphisms among human herpesvirus-6 isolates from North American infants. Virology 190: 490–493
11. Aubin J-T, Agut H, Collandre H, Yamanishi K, Chandran B, Montagnier L, Huraux J-M (1993) Antigenic and genetic differentiation of two putative types of human herpesvirus-6. J Virol Methods (in press)
12. Josephs SF, Ablashi DV, Salahuddin SZ, Kramarsky B, Franza BR, Pellett P, Buchbinder A, Memon S, Wong-Staal F, Gallo RC (1988) Molecular studies of HHV-6. J Virol Methods 21: 179–190
13. Frenkel N, Schirmer EC, Wyatt LS, Katsafanas G, Roffman E, Danovich RM, June CH (1990) Isolation of a new herpesvirus from human $CD4^+$ T cells. Proc Natl Acad Sci USA 87: 748–752
14. Gompels UA, Carrigan D, Carss AL, Arno J (1993) Two groups of human herpesvirus-6 identified by sequence analyses of laboratory strains and variants from Hodgkins lymphoma and bone marrow transplant patients. J Gen Virol (in press)
15. Teo IA, Griffin BE, Jones MD (1991) Characterisation of the DNA polymerase gene of human herpesvirus-6. J Virol 65: 4670–4680
16. Chou SW, Marousek GI (1992) Homology of the envelope glycoprotein B of human herpesvirus-6 and cytomegalovirus. Virology 191: 523–528
17. Gompels UA, Carss AL, Sun N, Arrand J (1992) Infectivity determinants encoded in a conserved gene block of human herpesvirus-6. DNA Sequence 3: 25–39
18. Sample J, Young L, Martin B, Chatman T, Keiff E, Rickinson A, Kieff E (1990) Epstein Barr virus types 1 and 2 differ in their EBNA-3A, EBNA-3B, and EBNA-3C genes. J Virol 69: 4084–4092

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