EMERGING HUMAN PATHOGENS HUMAN HERPES VIRUS-6 (HHV-6) & HUMAN HERPES VIRUS-7 (HHV-7)

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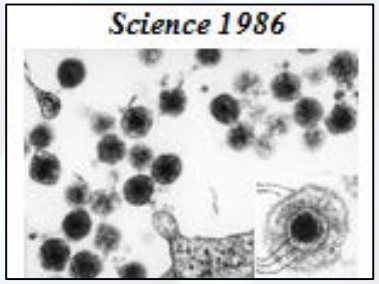
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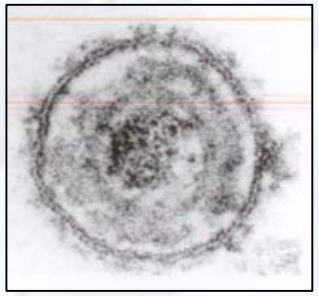
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DISCOVERY OF HHV-6 & HHV-7 WHICH BELONGS TO HUMAN BETA HERPESVIRUSES GENUS ROSEOLOVIRUS



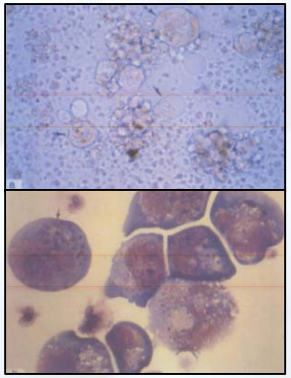
- A herpes virus called HBLV was isolated in 1986 from patients with lymphoproliferative disorders including AIDS and lymphoma in Dr. Robert Gallo's lab at NCI/NIH, Bethesda, MD (Salahuddin, Ablashi et al. (Science, 1986)
- Later it was renamed as HHV-6 (Ablashi et al. nature)
- HHV-6 was recognized to have two distinct variants HHV-6A and variant HHV-6B and eventually W.H.O. ICTV recognized them as two distinct human beta herpesviruses (Ablashi et al. 1993 Arch. Virology, Ablashi et al. 2014 Arch. Virology)
- A T-lymphotropic human herpesvirus, HHV-7, was isolated from a healthy individual by Dr. Niza Frenkel at NIAIDS/NIH in 1990 (Frenkel et al. 1990, PNAS)

Transmission & Epidemiology of HHV-6A, HHV-6B and HHV-7

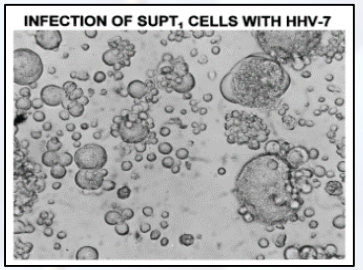
- They are ubiquitous viruses with horizontal infection, commonly occurring during infancy. They initiate infection through respiratory pathway, including lymphocyte-rich tonsils and olfactory ensheathing cells present in the nasal cavity
- HHV-6B can be isolated or transmitted through saliva and PBMC's. HHV-6A is rarely isolated from saliva, but more often from PBMC's
- Between .2 and .85% of the population in the USA, Canada, Europe and Japan carry inherited chromosomally integrated HHV-6A (ciHHV-6A) or HHV-6B (ciHHV-6B) through the germline from one of the parent
- HHV-6A, HHV-6B, HHV-7 antibody distribution is variable. >96% have HHV-6B acquired in early childhood and HHV-6A found later in life. HHV-7 antibody ranges 42% to 95% (Herpesviruses 6 and 7, by Yamanishi et al. 2014, Chapter in Field's Virology and Agub et al. 2015, Clinical Medical Review #2)

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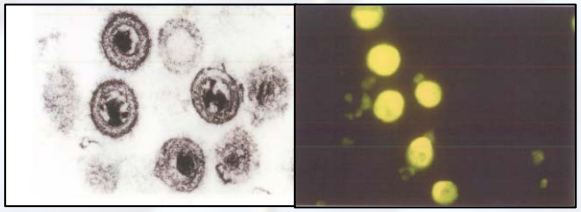
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GENOME, CELL BIOLOGY, CELLULAR RECEPTORS FOR HHV-6 & HHV-7



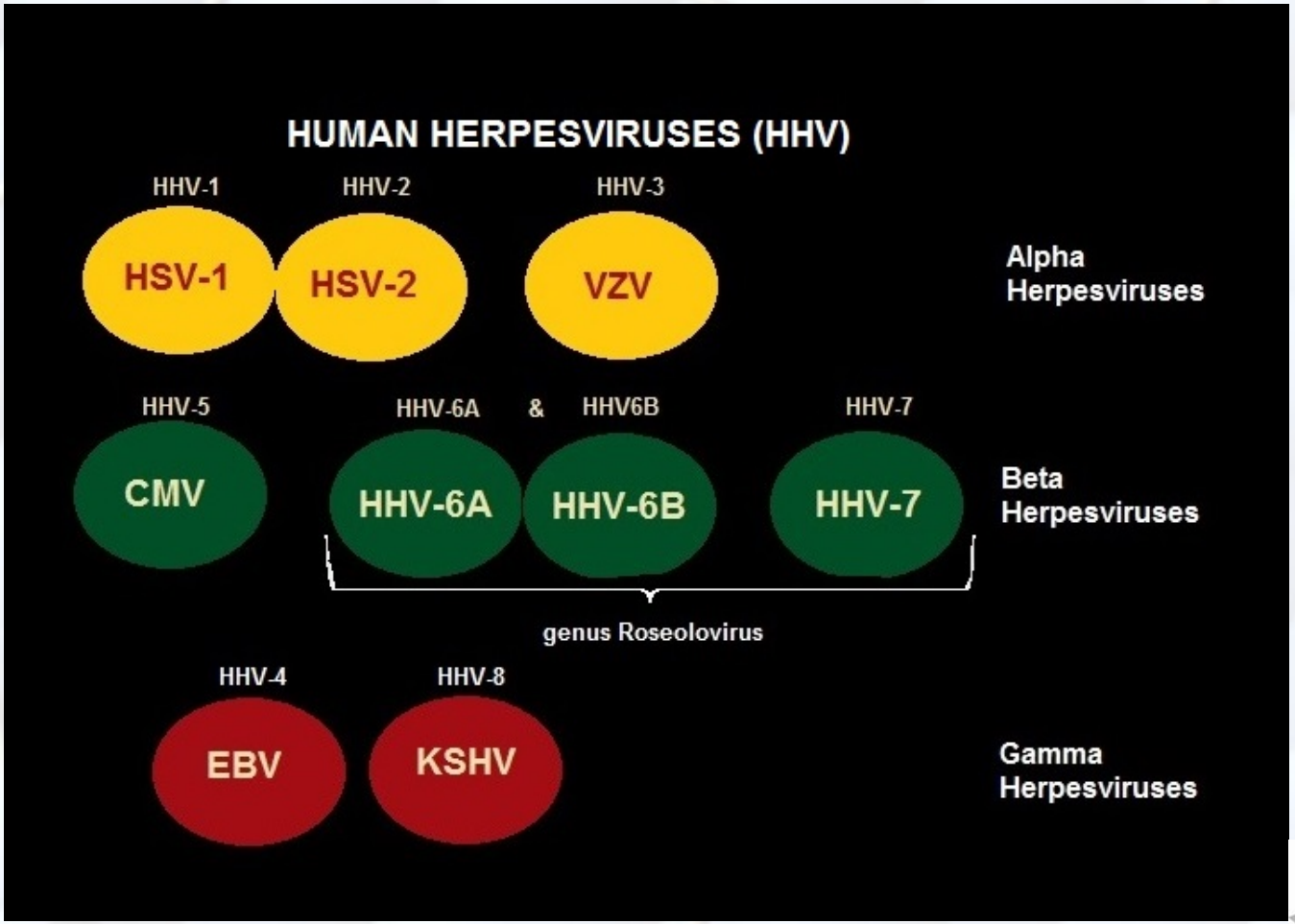
- Genome size of HHV-6 :162-170kb. Based on comparison of few isolates i.e. strains GS of HHV-6A, strain U1102 of HHV-6A and strains HST and Z-29 of HHV-6B
- Genome size of HHV-7 :145kb. (Based on two isolates RK and J1)
- DR3, U6, U83 and U94 are unique and encoded by HHV-6A and B and not HHV-7. Nine HHV-6A ORFS do not have HHV-6B and 9 HHV-6B ORFS have no HHV-6A counterpart
- Cell receptor for HHV-6A is CD46 (also for measles virus) cellular receptor HHV-6B is CD134 also called OX40 which is a member of the TNF. HHV-7uses CD4 as receptor, though virus infect cells which do not express CD4.
- HHV-6 A & B infect and replicate in a variety of cells e.g. lymphocytes, fibroblasts, neural cells like astrocytes, megakaryocytes, glioblastoma cell lines, peripheral blood monocytes, NK cells epithelial cells. (Ablashi et al., 1988, Intl Journal of Cancer)
- HHV-7 has a narrow in-vitro cell tropism thus far it is restricted either to PHA stimulated human cord blood mononuclear cells or replicate in a continuous cell line (Supt.) (Berneman et al. 1992 PNAS)
- Both HHV-6 and HHV-7 produce cytopathic effects when replicating in cell lines or PBMC's or CBMC's. Infected cells forming cluster and becomes balloon shaped enlarged cells, mostly multinucleated. (See the figure)
- Both HHV-6 and HHV-7 are highly cell associated and release very little virus in the cell culture supernatant. ($\geq$ one log)
- It was shown *in vitro* that HHV-7 activates HHV-6 (Reported by Dr. Frenkel)
- Both ciHHV6A AND ciHHV6B are chromosomally integrated at the telomere, and show that virus become latent and can be activated both *in vitro* and *in vivo*



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NOMENCLATURE OF HUMAN HERPES VIRUSES (AS OF 2013)



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PATHOGENESIS OF HHV-6A AND HHV-6B IN HUMAN DISEASES

ESTABLISHED ASSOCIATIONS:

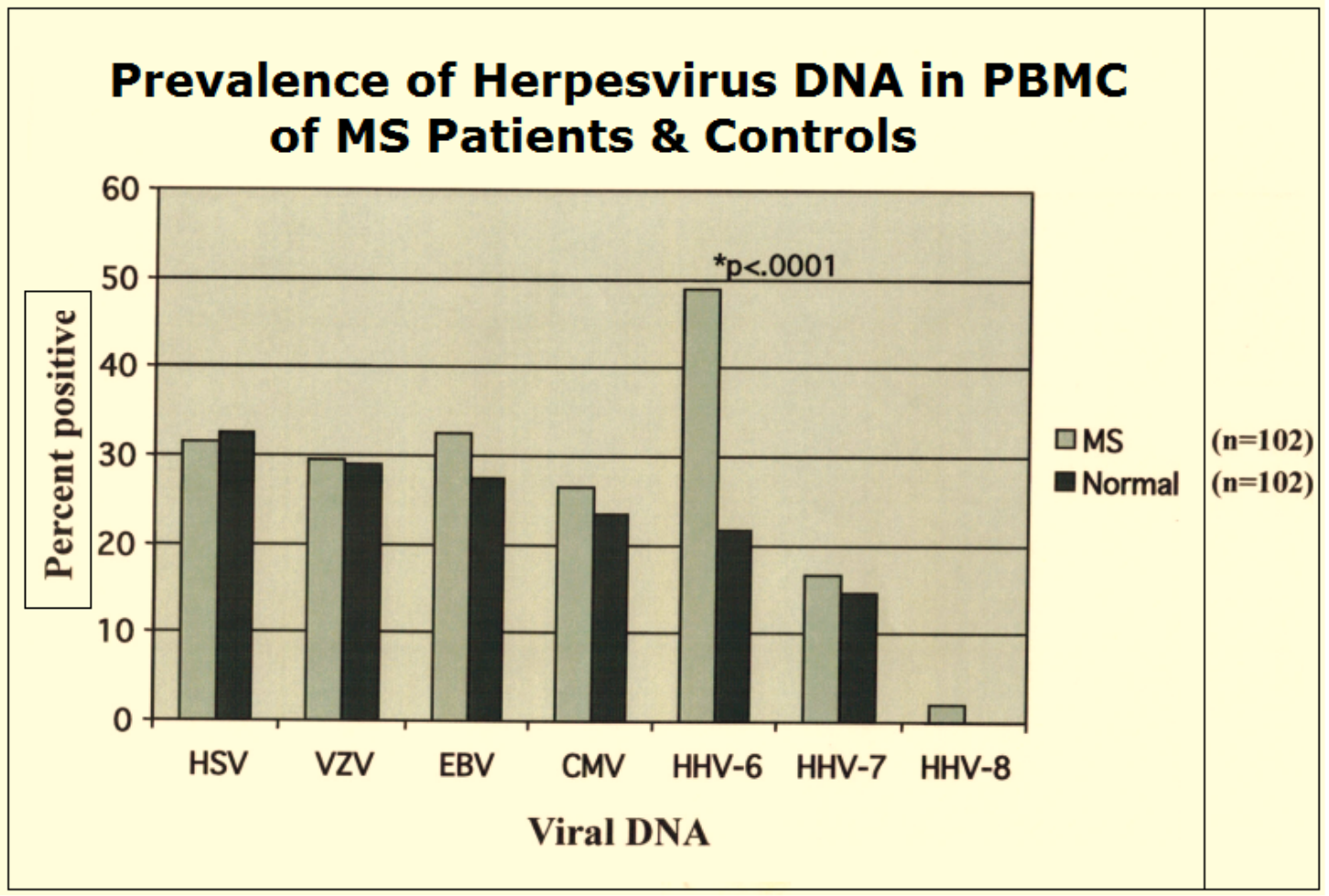
- Exanthema subitum (primary infection) mostly with HHV-6B
- Febrile seizures (primary infection) representing 5-15% of hospital visits
- Post transplant HHV-6B Acute Limbic Encephalitis (1-3% of HSCT and 8-10% of CBT patients)
- Febrile status epilepticus (reactivated and primary infection) in 32% of cases
- Drug induced hypersensitivity syndrome (HHV-6 reactivates in most severe cases)
- Interstitial pneumonitis in transplant patients
- Cardiomyopathy and heart failure
- CNS dysfunction & Delirium in transplant patients
- Bone marrow suppression
- Active necrotizing hepatitis (acute primary infection and transplant patients)
- Non-EBV mononucleosis (heterophile negative) in 3-8% of cases

POSSIBLE ASSOCIATIONS:

- HHV-6A & Hashimoto's thyroiditis
- Pneumonia in transplant patients
- Cancers: nodular sclerosis subset of Hodgkin's, gliomas, oral cancer, cervical cancer (co-factor)
- Connective tissue diseases e.g. scleroderma, lupus erythematosus.
- HHV-6 & multiple sclerosis (found in serum during relapse; HHV-6A specific oligoclonal bands)
- Mesial temporal lobe epilepsy (abortive infection/glutamate transport).
- Chronic fatigue syndrome (in a subset of patients with chronic microglial inflammation?)
- Increased risk of angina for individuals with ciHHV-6
- Increased risk of GVHD and all-cause mortality in transplant patients

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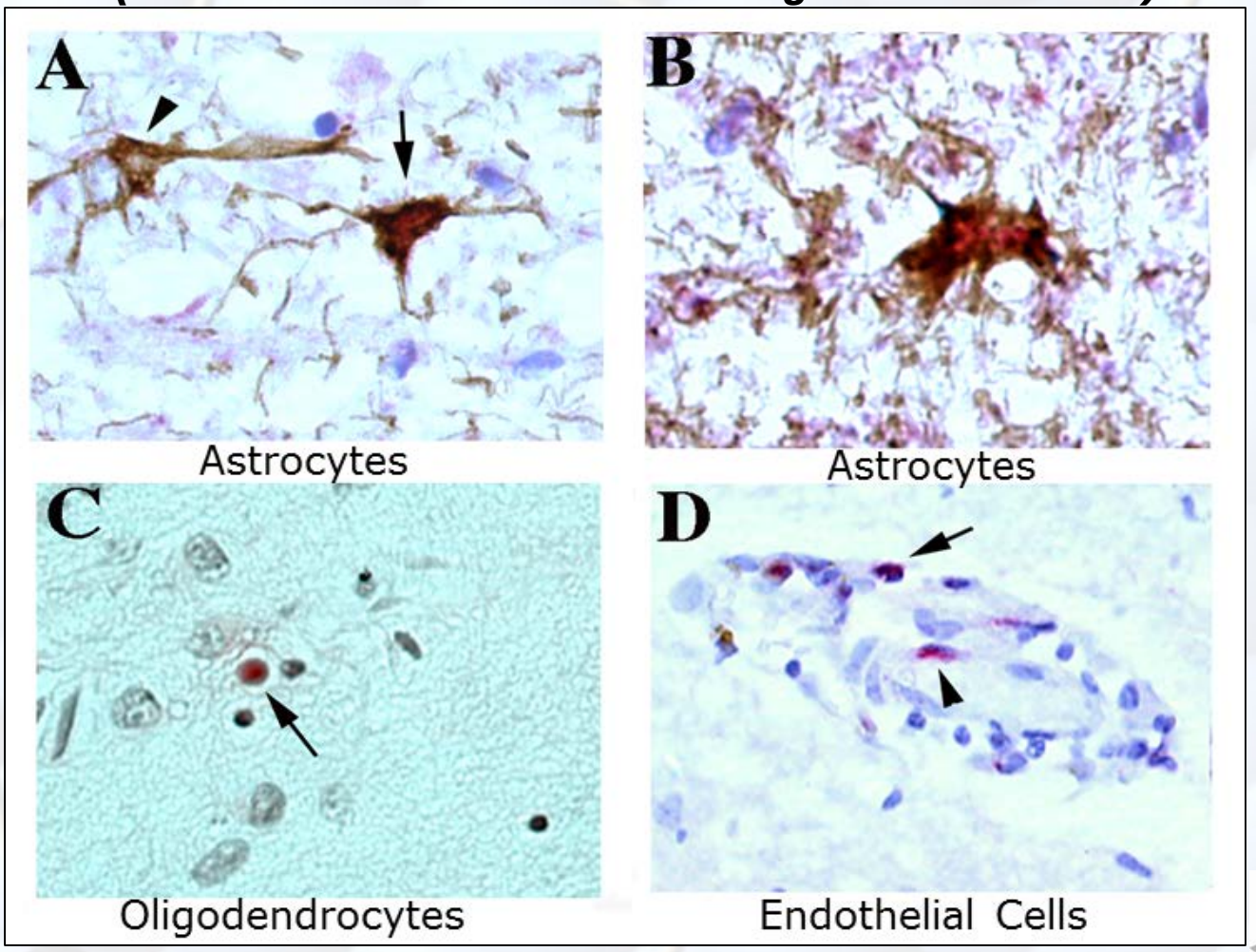
Alvarez-Lafuente, R., et al., Acta Neurol Scand 2002:105: 95-99

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HHV-6 VIRUS IN MS PLAQUES

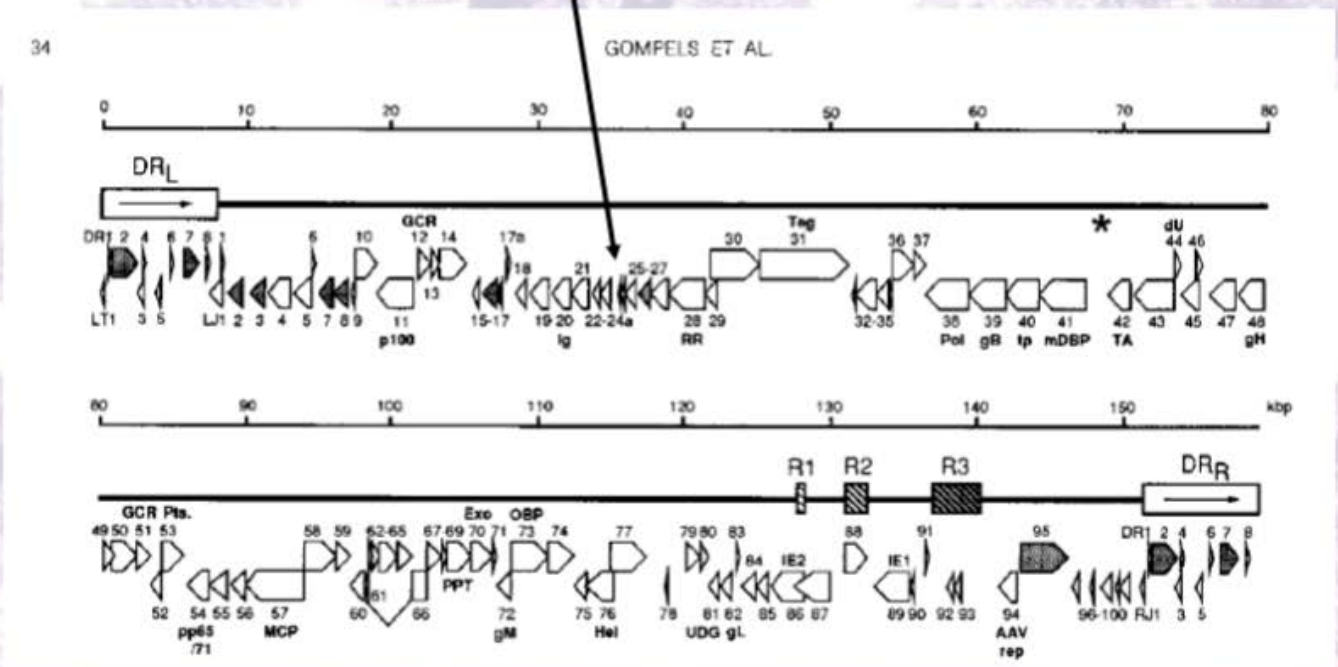
(arrows indicate HHV-6A antigen in red stain)



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Myelin basic protein DNA, sequence 96-102 is identical to HHV-6 DNA sequence U24, residues 4-10



HHV-6A gene sequence

SUMMARY OF HHV-6 IN MS

- Increased IgM to early HHV-6 antigens in RRMS
- Detection of HHV-6 DNA in serum and CSF of MS patients – predominantly HHV-6A-- during relapse but not remission
- Increased proliferative response to HHV-6A in PBL of MS patients
- HHV-6 specific oligoclonal bands in 20-25%
- CSF antibodies are directed to HHV-6A lytic protein
- Expression of HHV-6 proteins in active MS lesions
- Active HHV-6A associated with genetic polymorphism

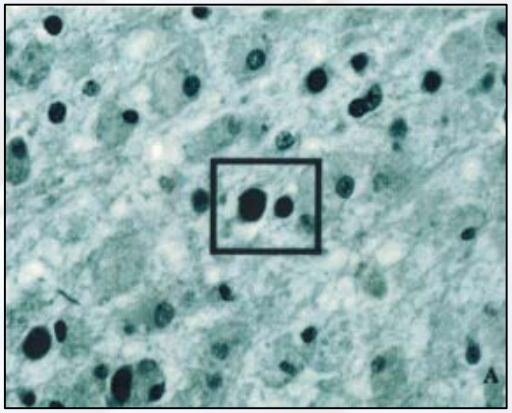
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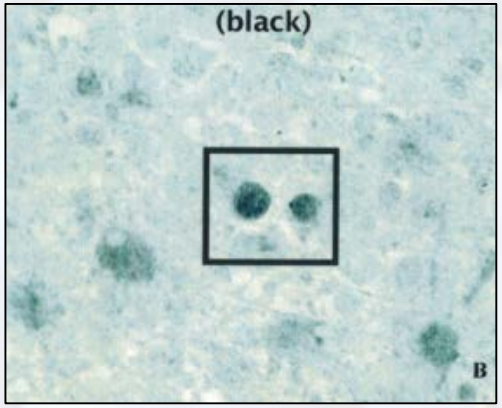
DETECTION OF HHV-6 IN PML BRAIN TISSUE

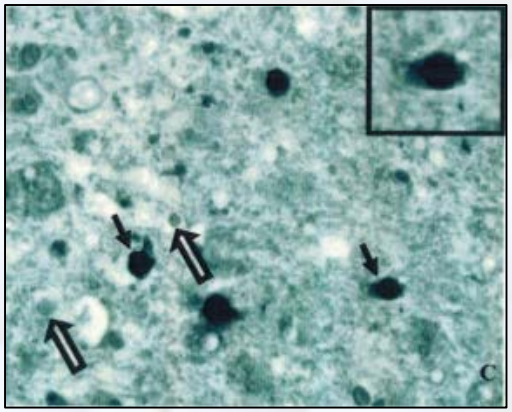
(Progressive Multifocal Leukoencephalopathy)
From Mock DJ, Goodman AD, Powers JM, Baker JV and Blumberg BM

H&E



HHV-6 p41 & p101





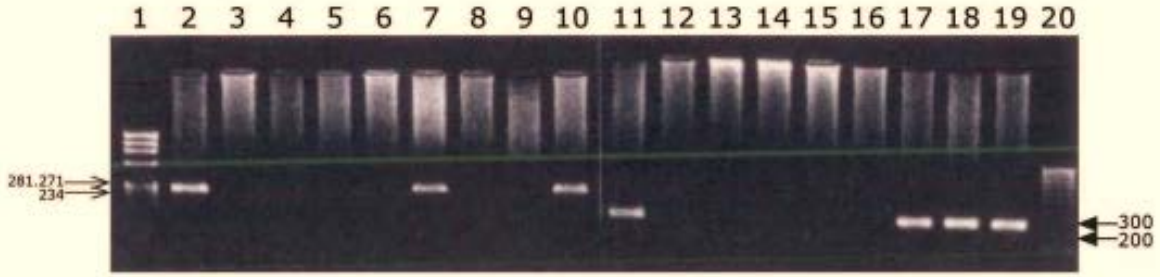
HHV-6 and JC virus co-localize in oligodendrocytes of PML brain

Figure 2. The first two slides in this series show two serial sections, taken four microns apart, from a case of PML. The H&E section on the left (figure 2a.) demonstrates several swollen oligodendrocytes characteristic of JC virus infection. In figure 2b., these same cells have been immunostained for HHV-6 p41 & p101 antigens demonstrating intense staining of the oligodendrocytes with lesser staining of some astrocytes. In the third panel (fig 2c.), co-infection of lesional oligodendrocyters was confirmed in the PML cases using double immunocytochemistry. ICC was first performed to the black reaction product and secondly with antibody to the JC virus large T antigen using AEC which gives an orange-red stain. Dual labeling appears as a brown signal in numerous swollen, lesional oligodendrocytes indicated by the large arrows and shown at higher magnification in the inset.

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REPRESENTATIVE RESULTS OF HHV-6 NESTED PCR ANALYSIS OF PLASMA AND CEREBRAL SPINAL FLUID SAMPLES FROM CHRONIC FATIGUE SYNDROME PATIENTS



Lane	Sample	PCR		Lane	Sample	PCR
1	X/Hae III DNA Marker			**11**	CSF **Sample:109-100-1**	**Positive**
2	**Plasma Sample:109-126-1**	**Positive**		12	Negative Control: CSF Perkin's Disease	Negative
3	Plasma Sample:109-126-14	Negative		13	CSF Sample:109-100-2	Negative
4	Plasma Sample:109-126-17	Negative		14	CSF Sample:109-100-3	Negative
5	Negative Controls: Plasma	Negative		15	CSF Sample:109-100-4	Negative
6	Plasma Sample:109-126-18	Negative		16	CSF Sample:109-100-5	Negative
7	**Plasma Sample:109-126-19**	**Positive**		**17**	CSF **Sample:109-100-6**	**Positive**
8	Plasma Sample:109-126-21	Negative		**18**	CSF **Sample:109-100-7**	**Positive**
9	Negative Controls: Plasma	Negative		**19**	CSF **Sample:109-100-8**	**Positive**
10	**Plasma Sample:109-126-22**	**Positive**		20	100bp DNA ladder	

***Note: These HHV-6 DNA'S were typed as Variant A**

Number PCR Positive: CFS 12/35 (34.2%)
Plasma 17/35 (48.6%)

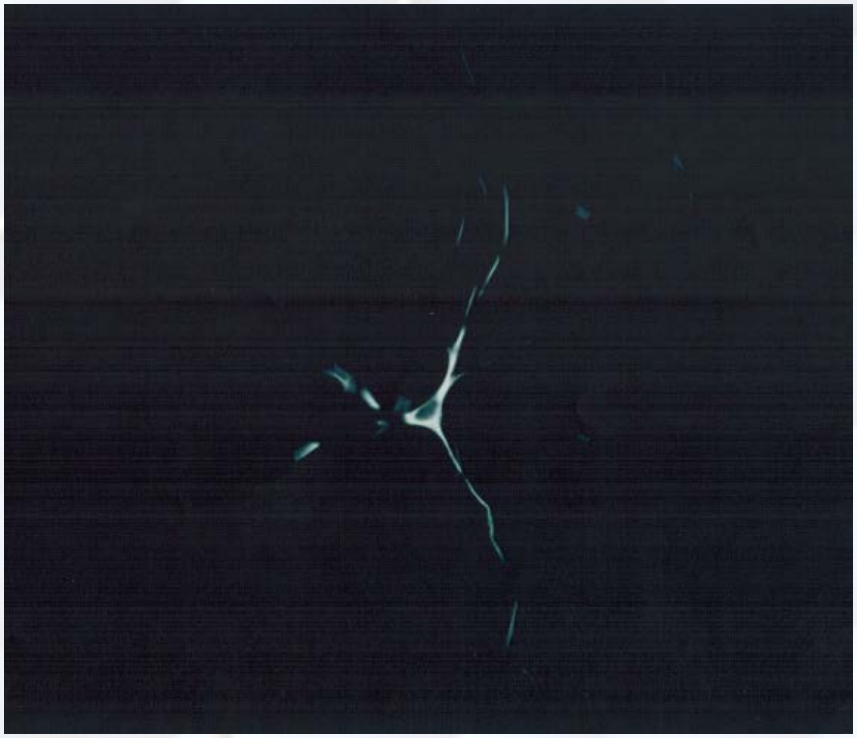
Used Nested PCR procedure & probe according to Dr. Steven Jacobson, NIH

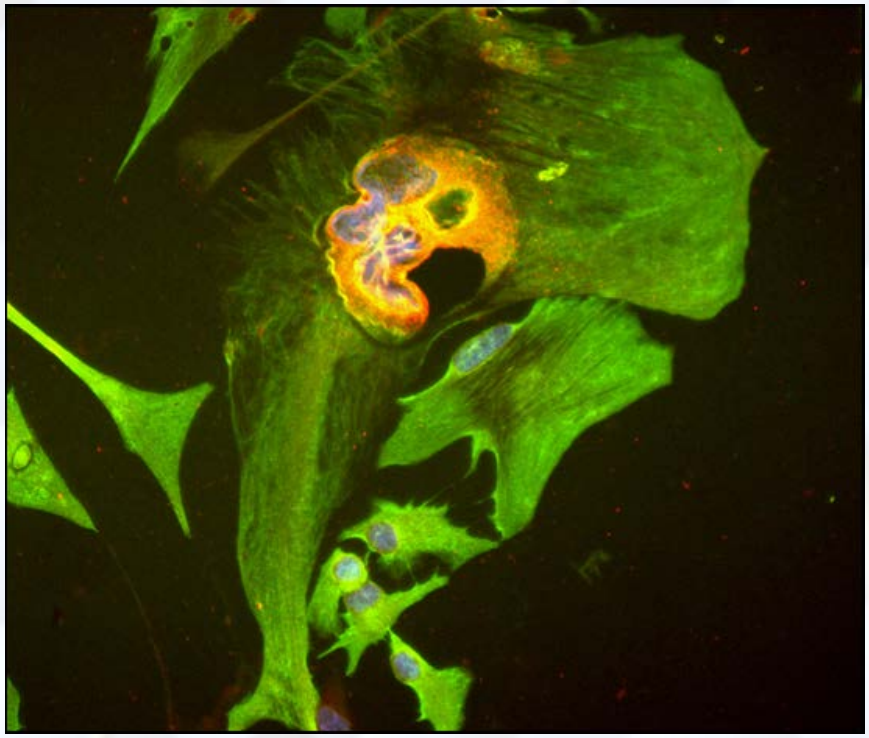
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ASTROCYTYES OBTAINED FROM MTLE LATERAL TEMPORAL LOBE INFECTED WITH HHV-6

GP116/64/54





Infected astrocyte

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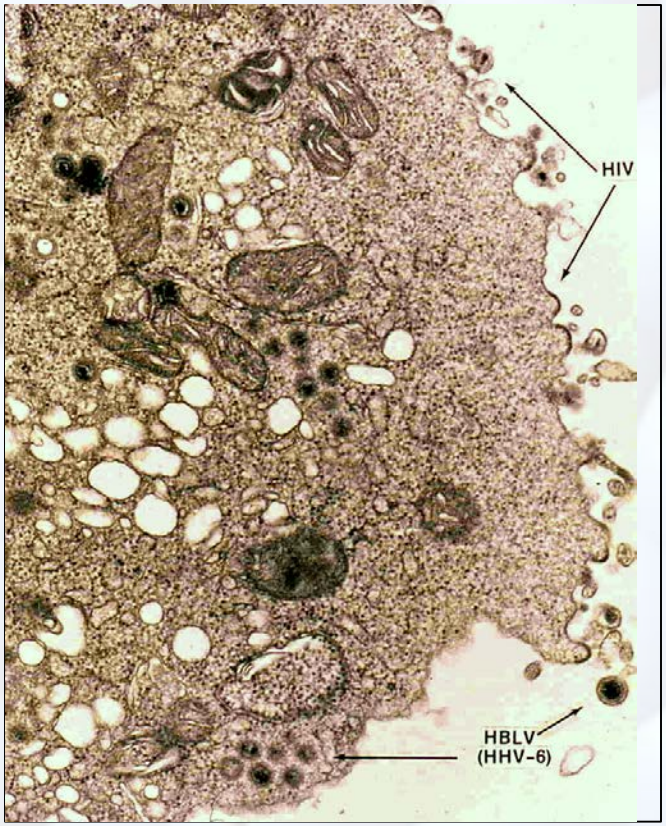
SUMMARY-EPILEPSY

- Surgical specimens from mesial temporal lobe epilepsy resections had very high HHV-6 viral loads compared to controls (Fotheringham 2007, Kawamura 2015)
- As in typical epilepsy, there is no inflammation at the site of surgery in the subset with a high HHV-6B viral load(Fotheringham 2007)
- Virus was localized to astrocytes in situ and cultured astrocytes also were demonstrated to express HHV-6 proteins ex vivo suggesting an active HHV-6 infection at the time of surgery (Fotheringham 2007)
- 32% of 100 febrile status epilepticus cases were caused by primary infection or reactivation of HHV-6B; 9% had HHV-7 (Epstein 2012)
- MCP-1 and GFAP were significantly higher in the samples with HHV-6DNA than those without viral DNA (Kawamura 2015)
- MTLE patients positive for ApoE4 have a higher viral load in their resections than those who are negative (Huang 2015)

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Viral Cooperation & HHV-6 / HIV-1 Co-Infection



Does HHV-6 play a Role in the Progression of HIV-1 infection to AIDS?

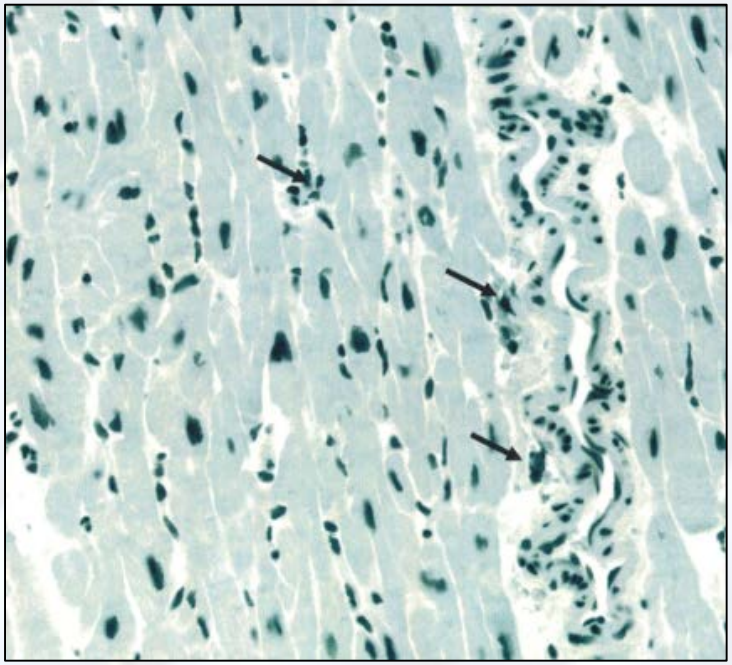
- The possible role of HHV-6, specially HHV-6A, in HIV infection is considered because **both viruses may infect CD4+ cells and HHV-6A can transactivate HIV LTR**
- **HHV-6A has been shown to alter cell membrane fluidity and receptor expression to facilitate HIV-1 co-infection** (Krueger GRF *et al.* AIDS Res Retrovir 1990 & Schonnebeck M *et al* In Vivo 1991*)*
- **HHV-6A can induce CD4 gene transcription and expression in CD4 negative cells, rendering them susceptible to HIV infection**. A marked association was seen between HHV-6A infection and progression of HIV pathogenicity in Thai children (Fields Virology – Ch. 64)
- Lusso *et al* published a report (Lancet 1991) on the **extent of HHV-6 infection in AIDS patients**; HHV-6 was found in the brain, salivary glands, myocardium, esophagus, bone marrow, spleen, tonsils, lymph nodes, spinal cord, adrenal glands pancreas, etc. (82% HHV-6 DNA using PCR (range 77-100%))
- **Co-infection** of macaques with **HHV-6A GS strain *and* SIV** resulted in rapid plasma viremia, transient clinical manifestation and seroconversion. Animals infected **with HHV-6 *alone* did not** demonstrate long-term clinical and immunological consequences. Animals infected with **SIV only** showed a progressive loss of CD4+ cells associated with the development of AIDS. However, animals **infected with both HHV-6 and SIV progressed rapidly to full-blown AIDS**. This suggests that HHV-6A infection may accelerate progression to AIDS in HIV infected individuals (Lusso *et al* PNAS 2007)

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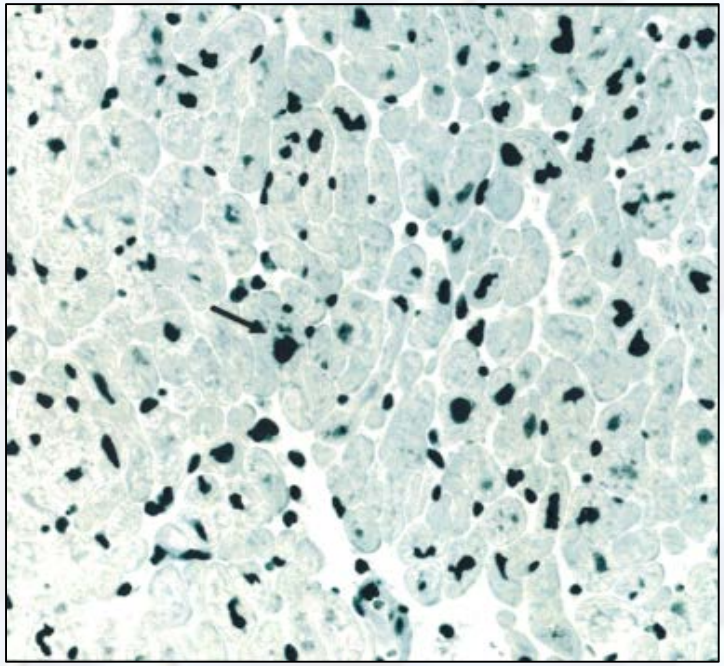
LOCALIZATION OF HHV-6 VARIANTS IN MYOCARDIAL TISSUE BY IHC

HHV-6 B



Detection of interstitial cells

HHV-6 A



Labeling of cardiomyocyte

Kühl et al.m, 2008

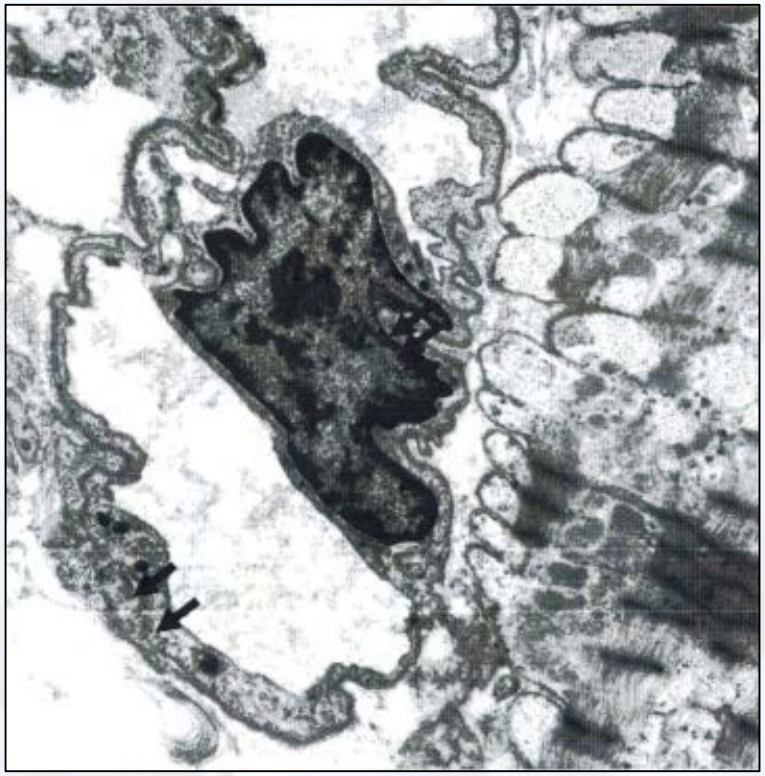
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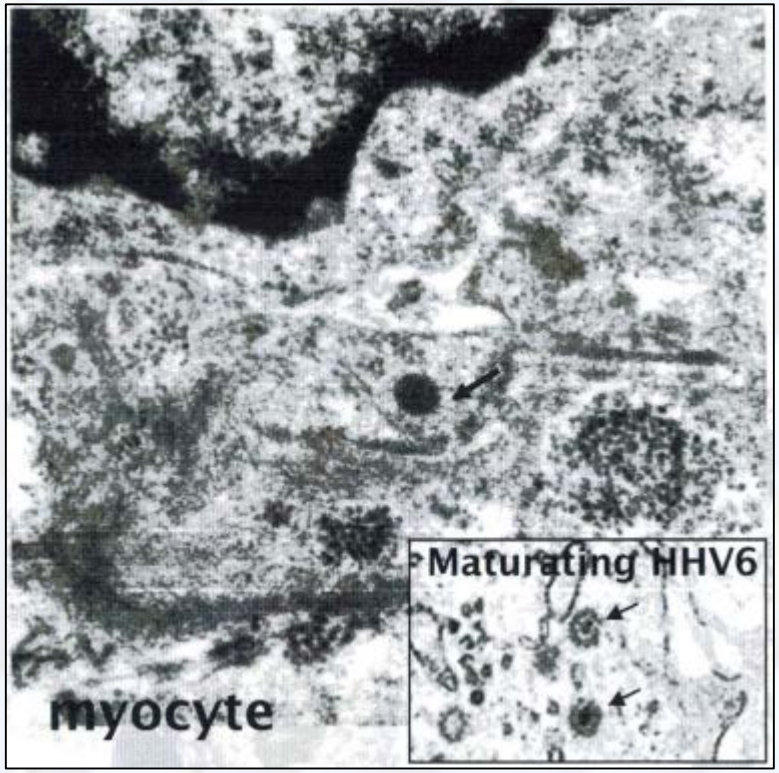
LOCALIZATION OF HHV-6 VARIANTS IN MYOCARDIAL TISSUE BY ELECTRON MICROSCOPY

HHV-6 B



Endothelium

HHV-6 A



Cardiomyocyte / EC

Kühl et al.m, 2014, published

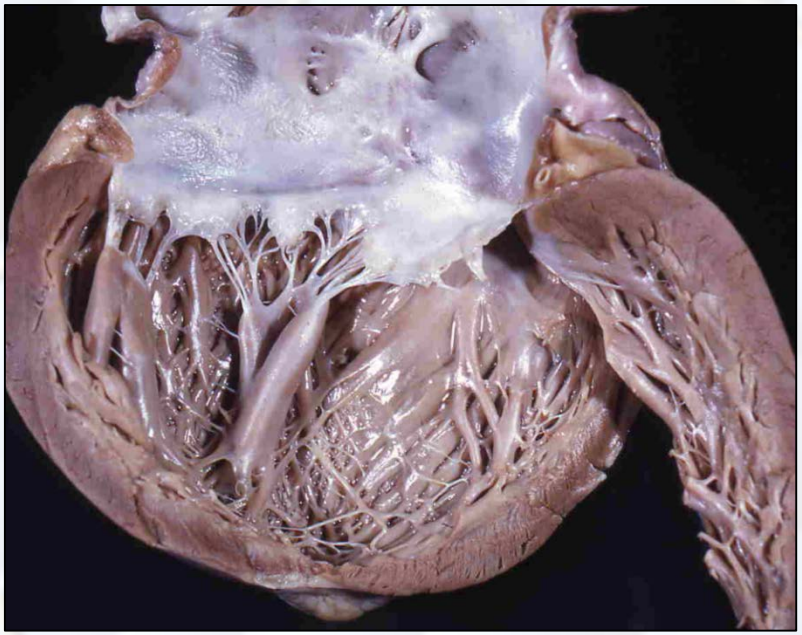
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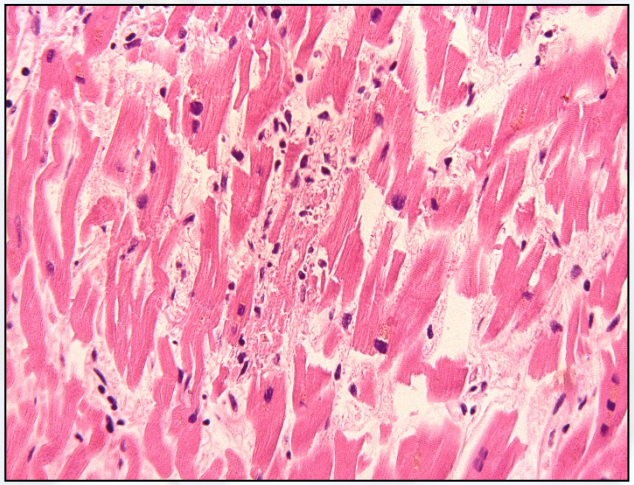
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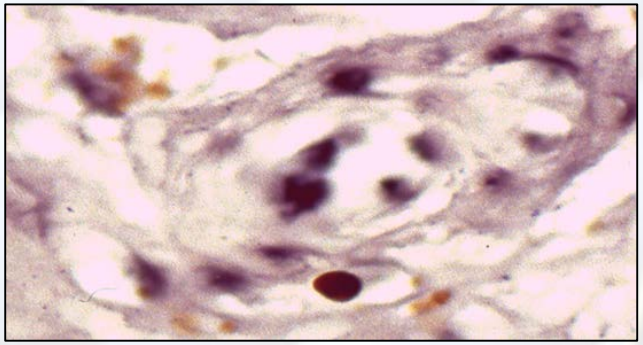
CARDIAC

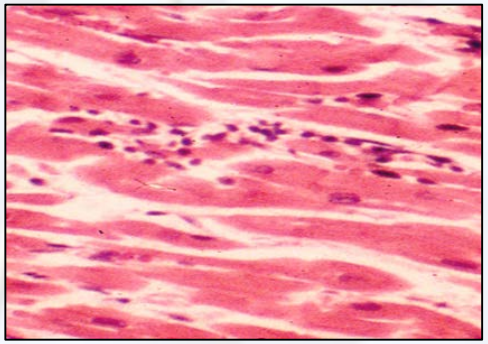
Myocarditis, dilated cardiomyopathy, coronary arteritis



54 years old patient with AIDS, dilated cardiomyopathy and persistent active HHV-6A infection





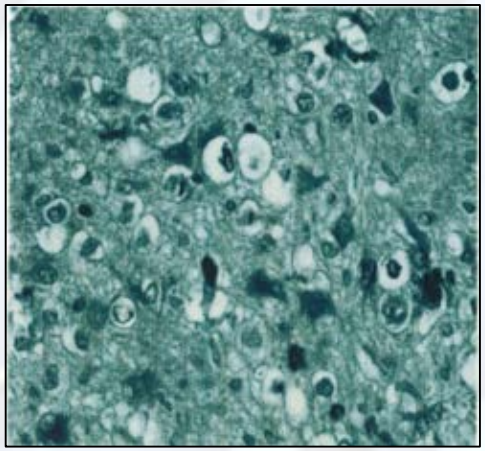


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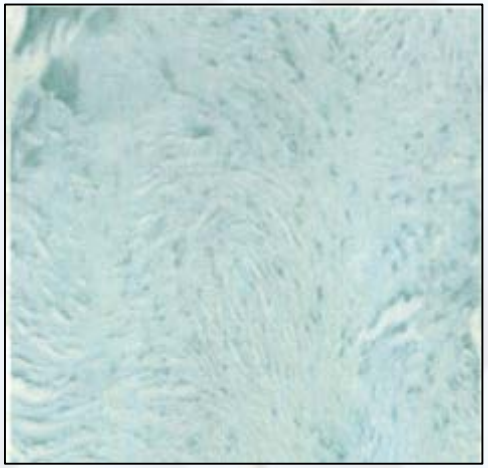
(Krueger GRF: 5TH International Conference HHV-6 & HHV-7; Barcelona, Spain, May 1-3, 2006)

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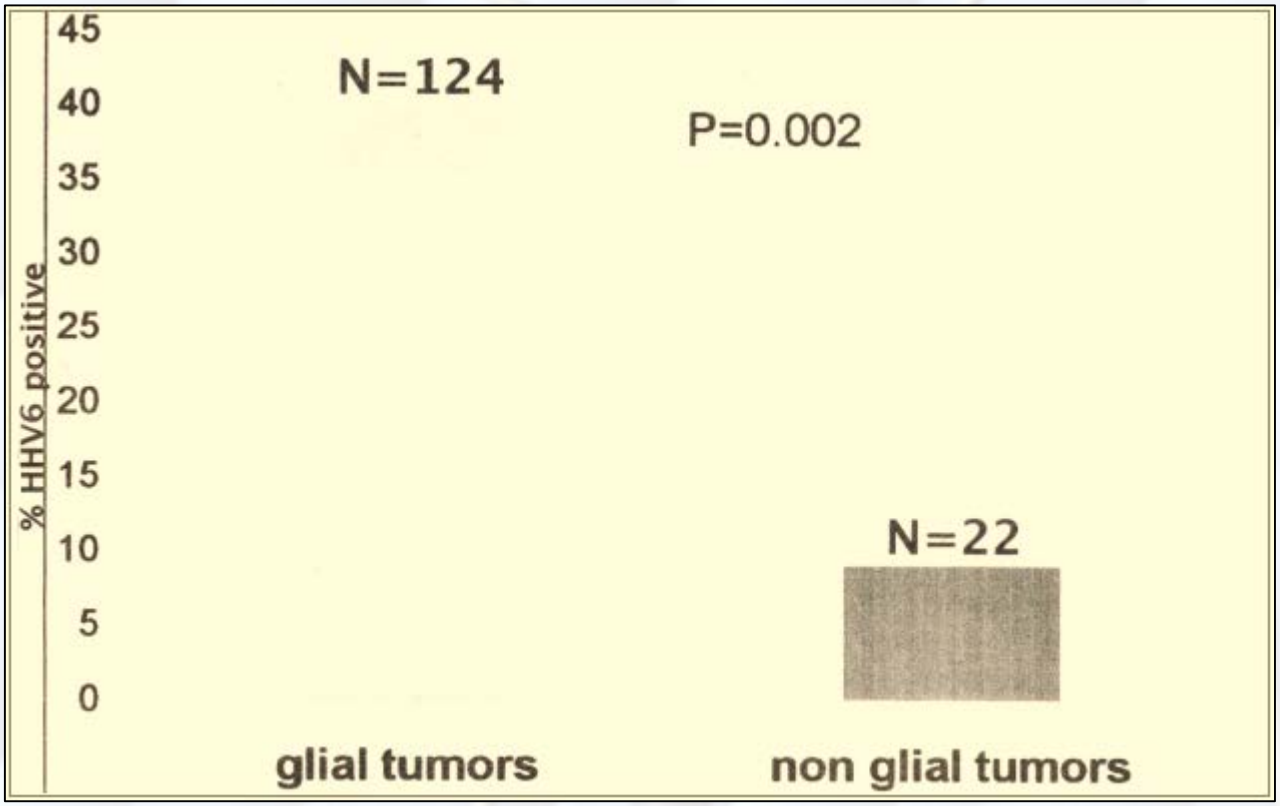
PREFERENTIAL DETECTION OF HUMAN HERPESVIRUS-6 GP116/64/54 ANTIGEN IN GLIAL TUMORS



Glial tumor



Non-glial tumor



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Crawford et. al

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SUMMARY OF BRAIN TUMORS

1. HHV-6 gene sequences are detected by nested PCR and *in situ* hybridization at a higher frequency than in age matched non-tumor brain and non-glial tumors

1. HHV-6 gp116/54/64 antigen measured by immunomicroscopy is present in 30% of pediatric gliomas and is not detected in non glial tumors

2. HHV-6 antibody staining appears to have a predilection for tumor tissue however it can be seen in adjacent tumor tissue at lower levels

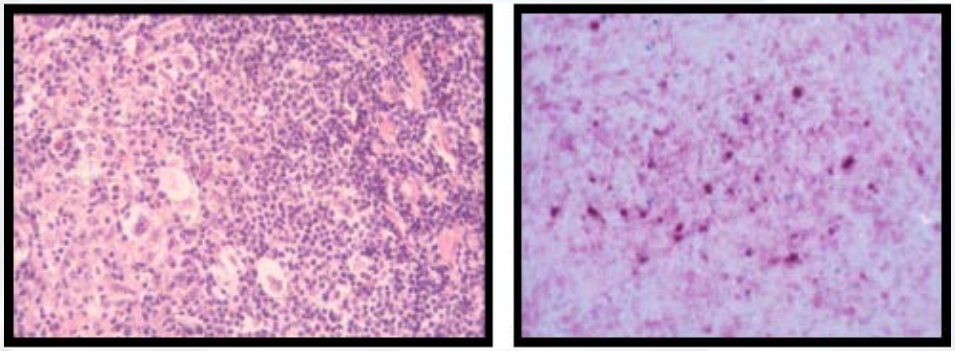
3. HHV-6 detection by IHC, nested PCR or ISH is not an independent prognostic indicator of survival in the series reported by Chinese study

4. HHV-6A DNA was deleted in $\geq$75% the gliomas reported in a Chinese study. They also isolated HHV-6A from glioma sample
   their findings have not been confirmed by other groups as yet.

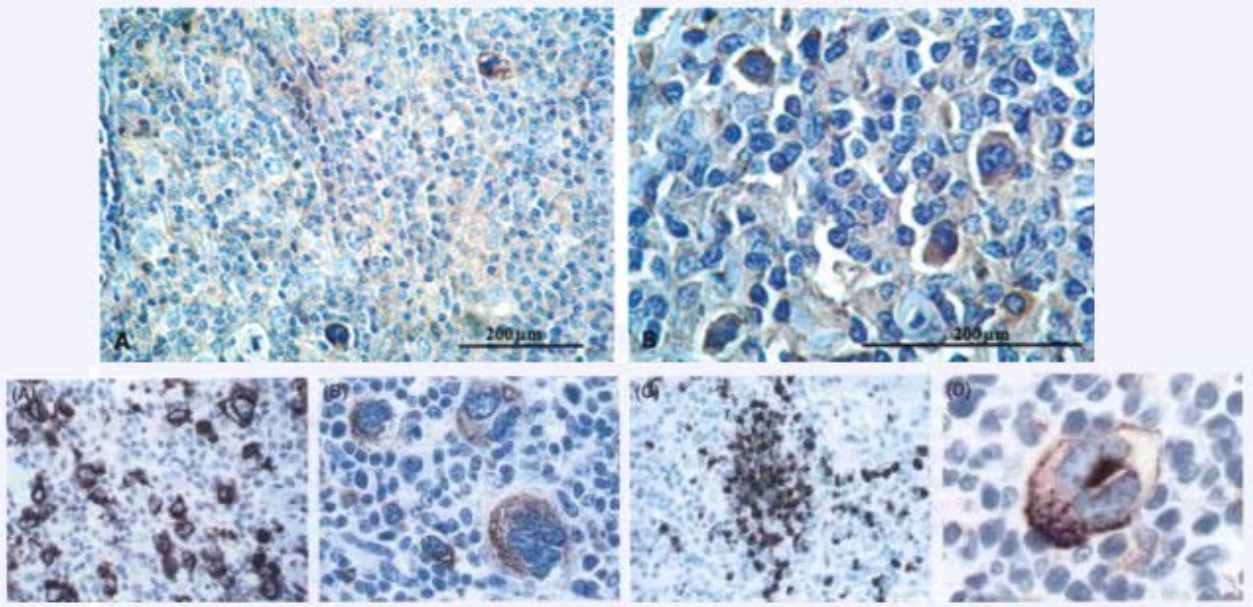
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HHV-6B IN HODGKIN'S DISEASE



Hodgkin's lymphoma, nodular sclerosing type: Left, H&E histology; Right HHV-6 DNA in situ hybridization (pZVH14)



HHV-6 IHC positivity of RS cells and reactive leucocytes in NSHL (A,B) Two cases of nodular sclerosis Hodgkin lymphoma (NSHL) with numerous HHV-6 positive Reed-Sternberg (RS) cells. (A) Original magnification x400; (B) Original magnification x600. (C) NSHL case with numerous HHV-6 positive small leucocytes. Original magnification x400. (D) A large binucleated RS cell in the centre of the image displaying golden brown CD30 staining of the cell membrane and Golgi zone, and deep purple granular HHV-6 staining in the cytoplasm. Original magnification x1000.

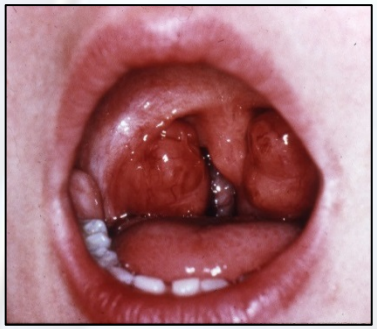
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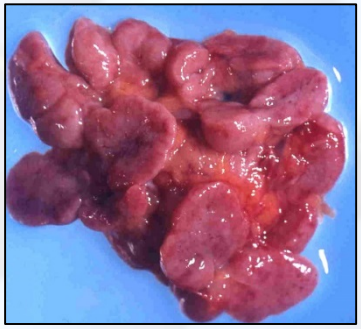
Provided by Gerhard Krueger, Sylvie Ranger-Rogez

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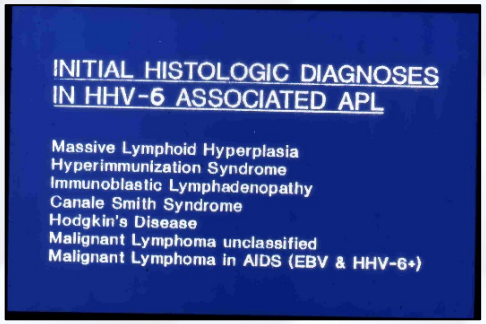
ATYPICAL POLYCLONAL LYMPHOPROLIFERATION (APL) HUMAN HERPESVIRUS-6

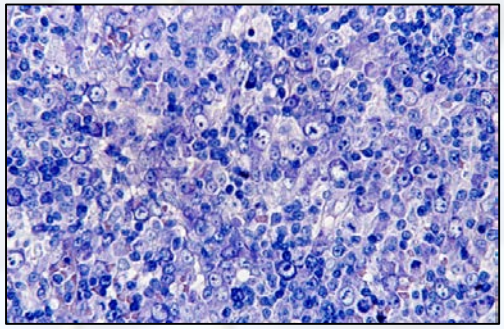
Atypical polyclonal lymphoproliferation (APL) alternatively "hyperimmunization lymphadenopathy" or chronic infectious mononucleosis-like disease



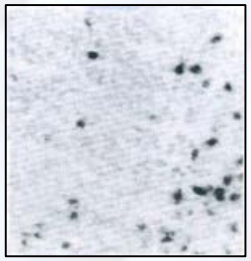


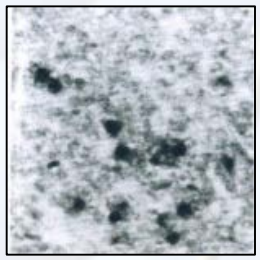
Persistent painless "tumorlike" enlargement of tonsils (left) or lymph notes (here Axillary lymph nodes; right) in persistently active HHV-6 (or EBV or both) infections





Histologic features of APL are variable (see differential diagnosis above left) mimicking infectious mononucleosis, Hodgkin's disease or pleomorphic lymphoma (above right and next page)



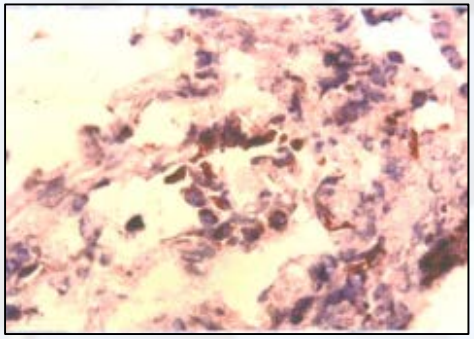


Examples of positive in situ hybridization for HHV-6 DNA in APL (pZVH14)

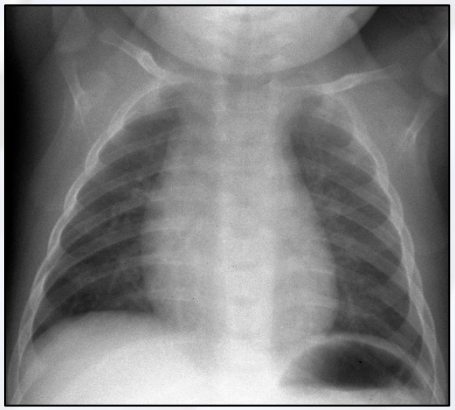
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TRANSPLANTATION – BONE MARROW, INTERSTITIAL PNEUMONITIS

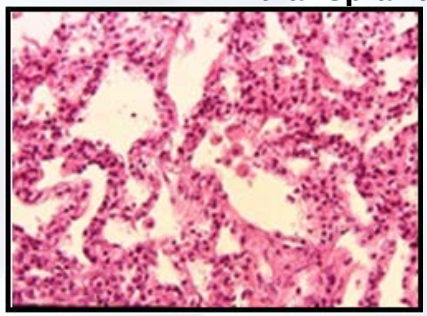


Immunohistochemistry for HHV-6 p41 on frozen section of lung biopsy

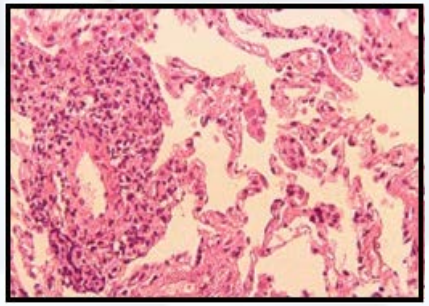




X-ray (left) and gross lung (right) of patient with interstitial pneumonia following bone marrow transplant and HHV-6 reactivation



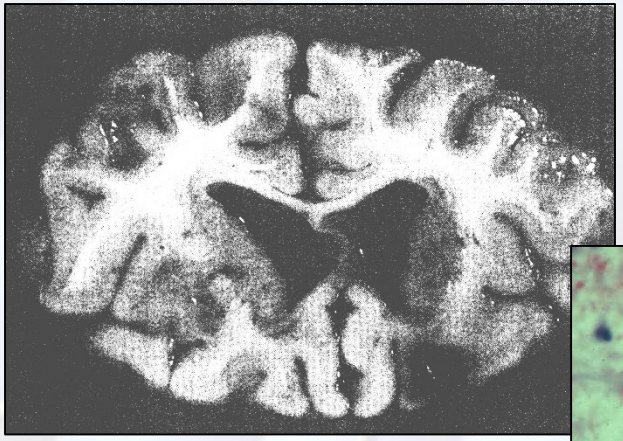
Non-specific interstitial pneumonitis (NSIP) following HHV-6 reactivation



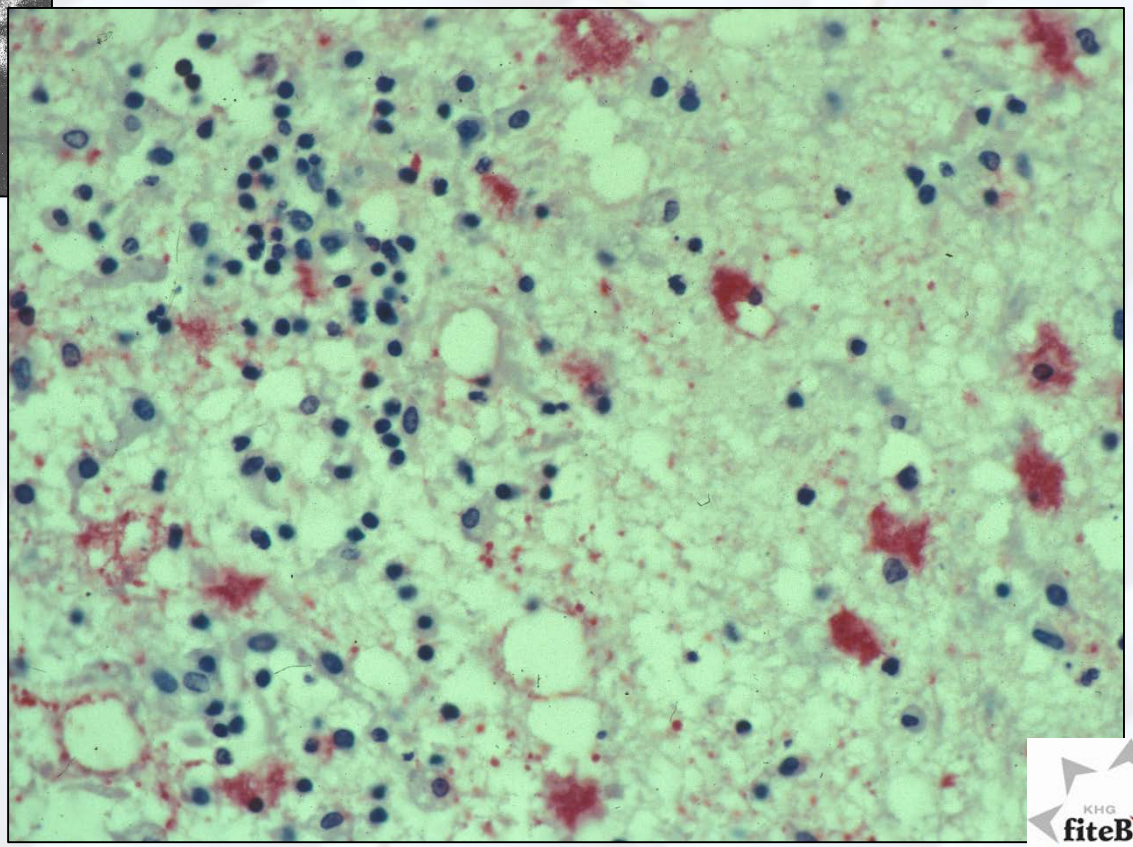
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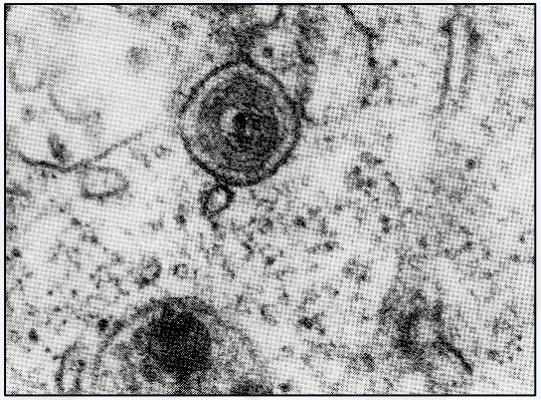
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HHV-6 IN IMMUNE DEFICIENCY



Acute necrotizing encephalitis in a child with Griscelli's syndrome





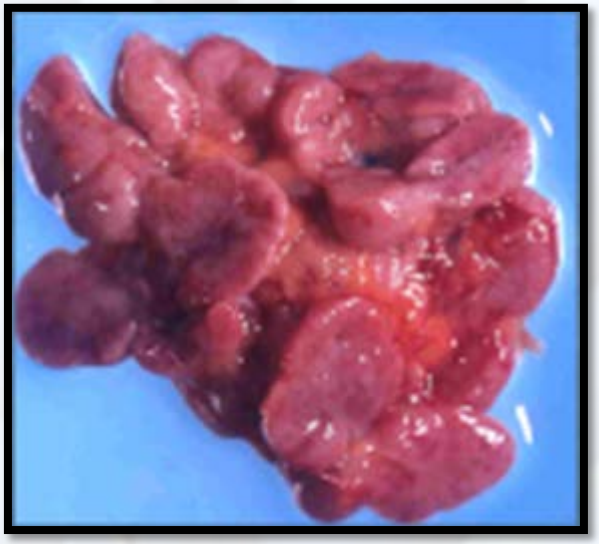
Red cells are HHV-6 p41 positive

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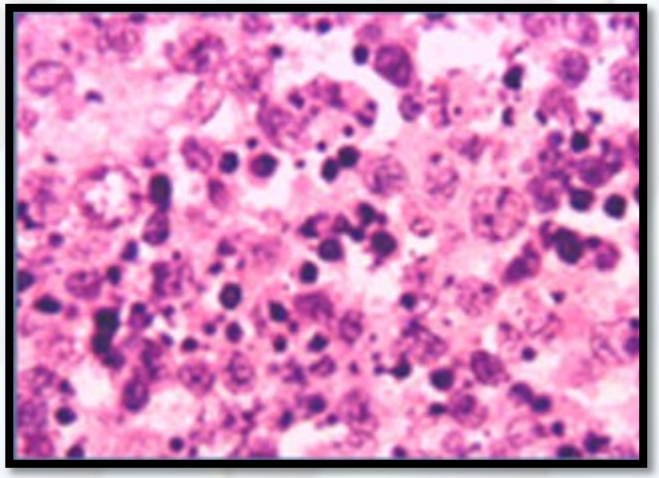
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Persistent Effects of Lymphotropic Herpesviruses

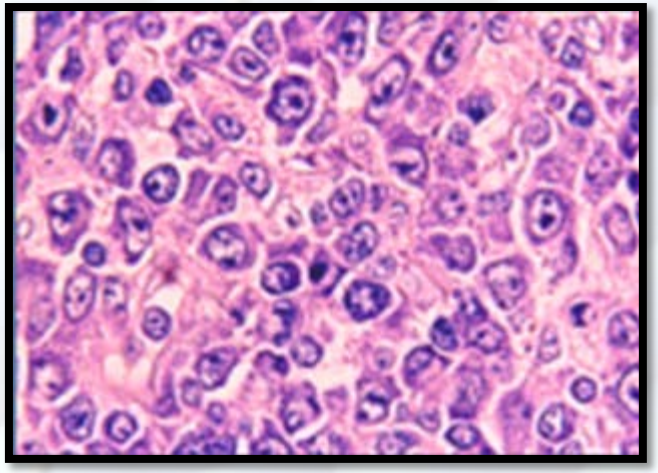




a) Kikuchi syndrome (apoptosis predominant)



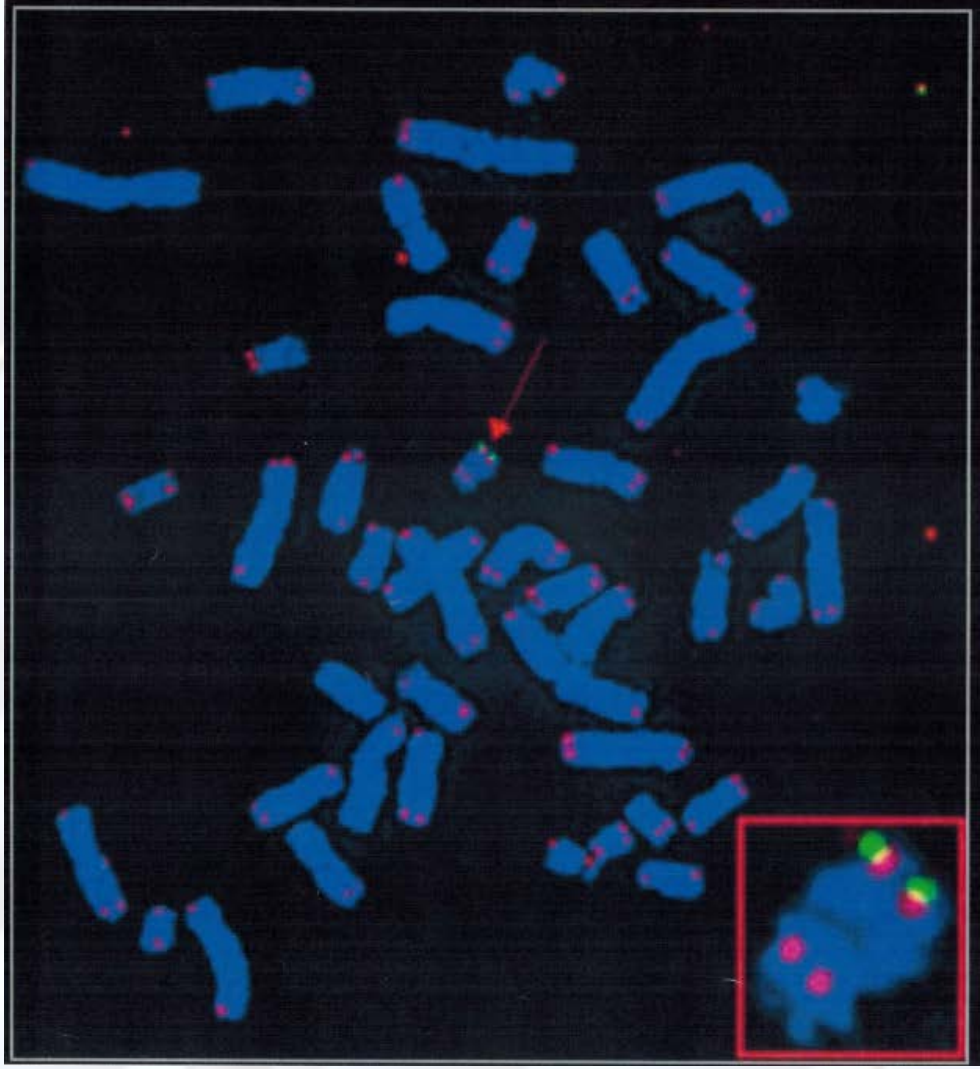
b) Progressive lymphoproliferative disorder (e.g. post transplant lymphoma)



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Presence of ciHHV-6 at chromosomal telomeres



Telomeres (red)

HHV-6 DNA (green)

DNA (blue).

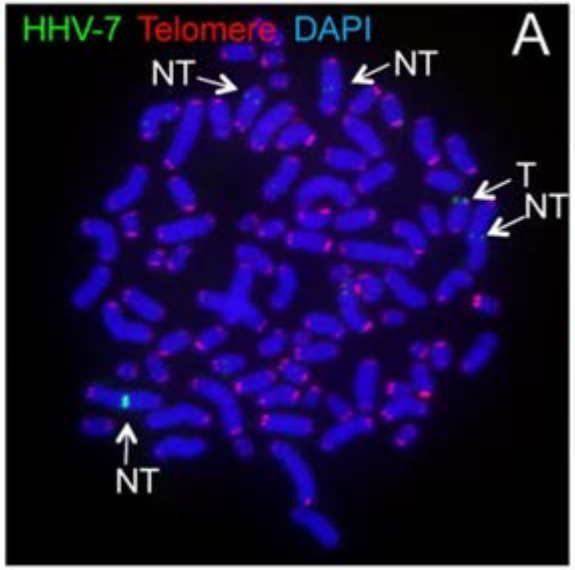
All ciHHV-6 members of the family represented here harbored HHV-6 genomes at a telomere of chromosome 22

From Arbuckle et al., PNAS 107:5563-5568,2010

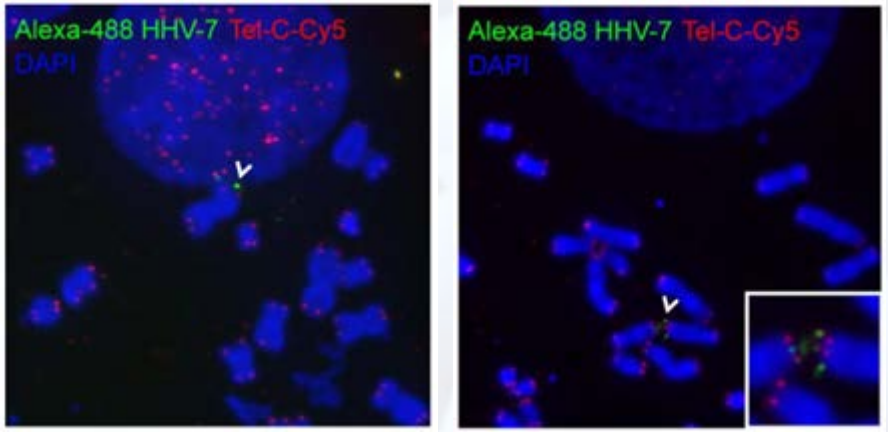
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FISH ANALYSIS SUPPORTS INTEGRATION OF HHV-7 DURING LYTIC INFECTION



SupT-1 cells with HHV-7 JI lytic infection



HEK cells with HHV-7 JI latent infection

- We have shown that HHV-7 possibility of acquired (not inherited) chromosomal integration during after lytic and latent infection
- Like HHV-6, HHV-7 integrates into telomeres
- Constant alterations within DR, in particularly within telomeric repeat sequences, during viral activation indicates potential role of telomeric repeats during viral activation
- This is the first study of ciHHV-7 (Un-published)

Work done by Prusty together with the Brain Consortium (USA) and Dr. Carla Toro (UK)
(Presented at the IHW Conference 2015 in USA)

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KEY POINTS CIHHV-6 & CIHHV-7

- Approximately 1% of the population harbors germline ciHHV-6
- Because it is transmitted via the germline, the HHV-6 genome is present in every nucleated cell in the body
- HHV-6 levels in whole blood >5.5 log10 copies/ml are suggestive of CiHHV-6
- ciHHV-6 transplant patients may be more likely to experience GVHD and bacterial infections
- Integrated HHV-6 can be activated in vitro
- ciHHV-6 can lead to the misdiagnosis of reactivated HHV-6 infection
- We have shown evidence for possibility of acquired chromosomal integration of HHV-7 during both lytic and latent infection (Un-published Bhupesh Prusty et al) presented at the IHW meeting 2015
- There is no evidence of ciHHV-7 inheritance or germline transmission like CiHHV-6A, and HHV-6B from Medveczky et al. HHV-6/HHV-7 Conference 2015 and (Hall 2004)

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ANTIVIRALS – FDA Approved

Drug name	Structure	Main use	Viral target	Status	In vitro activity against HHV-6
(Val) acyclovir	Nucleoside analogue	HSV, VZV	Polymerase	✓	Weak
(Val) ganciclovir	Nucleoside analogue	CMV	Polymerase	✓	Good
Penciclovir	Nucleoside analogue	HSV	Polymerase	✓	None
Cidofovir	Nucleotide analogue	CMV	Polymerase	✓	Good
Foscarnet	Pyrophosphate analogue	CMV	Polymerase	✓	Excellent

Courtesy of Lieve Naesens, Rega Institute

Undergoing FDA Approval Process

Drug name	Structure	Main use	Viral target	Status	In vitro activity against HHV-6
Brincidofovir (CMX001)	Nucleotide analogue	CMV, adenovirus	Polymerase	Phase 3	Excellent
Valomaciclovir (H2G)	Nucleoside analogue	EBV, VZV	Polymerase	Phase 2	Very good
Cyclopropavir	Nucleoside analogue	CMV	Polymerase + protein kinase	Phase 1	Excellent
Letermovir		CMV	Terminase	Phase 3	None
Maribavir		CMV	Protein kinase	Phase 2 (3)	None
Pritelivir		HSV-2	Helicase-primase	Phase 2	None

Courtesy of Lieve Naesens, Rega Institute

OTHER ANTIVIRALS

Compounds that work *in vitro* but are not being pursued by drug companies:

- Acyclic nucleoside phosphonate analogues
- CMV423
- Arylsulfone Derivatives
- 1-4-DIHYDROPYRIDINE DERIVATIVE
- Artesunate (anti-malarial drug)
- Ampligen (double-stranded mismatched RNA)
- K-21 (ready for safety tests in animals)

Compounds found to be effective *in vitro* by an HHV-6 Foundation study among 60 studied. The compounds with the most promise were found to be:

- Red marine algae
- Amantadine (Symmetrel) *high doses*
- Lamotrigine (Lamictal) – effective for HHV-6B only

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CONCLUSIONS

- HHV-6 prevalence is widespread throughout the world. However, the detection of >95% antibody to HHV-6 is more due to HHV-6B since at present, we do not have a serologic test to differentiate antibody directed to A or B
- The transmission of HHV-6 is horizontal but in <1% of the population, the inherited chromosomally integrated form can be transmitted through the germline where it is transmitted from parent to child
- HHV-6 could be very immunosuppressive and upregulate TNF-alpha, IL-Beta, TNF-Gamma, IL-10, IL-21 and downregulates complement activity through CD46 receptor
- HHV-6B is a common cause of limbic encephalitis in immunosuppressed individuals, and HHV-6A and HHV-6B have been associated with the pathogenesis of many diseases/disorders either directly or indirectly. The pathogenic role of HHV-7 is not well studied as yet, but can be associated with seizures and encephalitis
- HHV-6 is highly neurotropic and infects various neural cells that are associated with MS, MTLE, encephalitis which suggests a major contributory role in the etiology
- In transplantation (bone marrow, stem cell, kidney, liver), overexpression of HHV-6B could lead to enhancement of CMV disease, graft rejection, encephalitis, pneumonitis

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CONCLUSIONS (continued)

- Inoculation of HHV-6A in common marmosets leads to neurologic lesions identical to MS. Inoculation of HHV-6A in macaques with SIV leads to enhanced disease and faster progression toward death of inoculated animals

- Since HHV-6 can be detectable in PBMCs, saliva, CSF, plasma/serum in patients and some cases in healthy, either quantitation of viral load (DNA copies) or elevated antibody would be needed to see HHV-6 reactivation

- Detection of HHV-6 DNA or antigen in disease tissues by IHC is a good indicator of reactivation and allows identification of the cell types where viral replication and latency occurs

- *In vitro* studies show that some antivirals are good inhibitors of HHV-6 infection; however, the sensitivity of inhibition may vary between HHV-6A and B. Antivirals currently used *in vivo* to treat HHV-6 infection include foscarnet, ganciclovir (Valcyte). A more potent antiviral, brincidofovir is expected to be approved soon

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ACKNOWLEDGEMENTS

- Dirk Lassner, PhD, Cardiac Diagnosis Treatment Institute, Berlin, Germany
- Steve Jacobson, PhD, NIH, Bethesda, MD, USA
- Paolo Lusso, MD, PhD, NIH, Bethesda, MD, USA
- Louis Flamond, PhD, University Laval, Quebec, Canada
- Peter Medveczky, MD., University of East Florida, Tampa, FL, USA
- Lieve Naesen, PhD, Leuven, Belgium
- Ursula Gompels, PhD, University London, London, UK
- Daniel Peterson, MD., Incline Village, NV, USA
- Sophie Collot-Teixeira, Associate Clinical Sample Principal Scientist at AstraZeneca, Greater London, UK
- Susan Levine, MD., New York, NY, USA
- Tetsushi Yoshikawa, MD., PhD, Fujika Health University, Aichi, Japan
- Yasuko Mori, MD., PhD, Kobi University Medical School, Kobe, Japan
- Koichi Yamanishi, MD., PhD, Osaka University Foundation, Osaka, Japan
- Michael Scheurer, PhD, Baylor College of Medicine, Houston, TX, USA
- Philip Pellett, MD., PhD, Wayne State University School of Medicine, Detroit, MI, USA
- Jin Mei Li, West China Hospital, Department of Neurology, Chengdu, China
- Mario Luppi, MD., PhD, Department Medicine Oncology, Modena, Italy
- Emily Leibovitch, PhD., NIH, Bethesda, MD, USA
- Konstance Knox, PhD., Institute of Viral Pathogenesis, Milwaukee, WI, USA
- David Hundall, MD., Department of Pathology, Yale University School of Medicine, New Haven, CT, USA
- Sylvie Ranger-Rogez, Université de Limoges, Faculty of Pharmacy, Limoges, France
- Andrew Goodman, MD., Department of Neurology, University of Rochester, Rochester, NY, USA
- Leon Epstein, MD., PhD., Virology Dept. Groupe Hospital Univ. Paris, Est., Paris, France
- Jesse Arbuckle, PhD., NIH, Bethesda, MD, USA
- Dario Deluca, PhD., Department of Experimental Medicine, University of Ferrara, Ferrara, Italy
- Niza Frenkel, PhD., Chair Mol. Virology, Tel Aviv. Univ. of Israel
- Robert Gallo, MD., Inst. Human Virology, Univ. of Maryland Medical School, Baltimore, MD, USA
- Anthony Komaroff, MD., Department of Medicine Harvard Medical School, Boston, MA, USA
- Sheryl Lunsford, HHV-6 Foundation, Santa Barbara, CA, USA
- Elaine O'Leary, KHG fiteBac® Technology, Marietta, GA, USA

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