The latent human herpesvirus-6A genome specifically integrates in telomeres of human chromosomes in vivo and in vitro

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Virus-host DNA exchange in humans

If we compare known virus genomes with individual human genomes we find a large number of homologous regions.

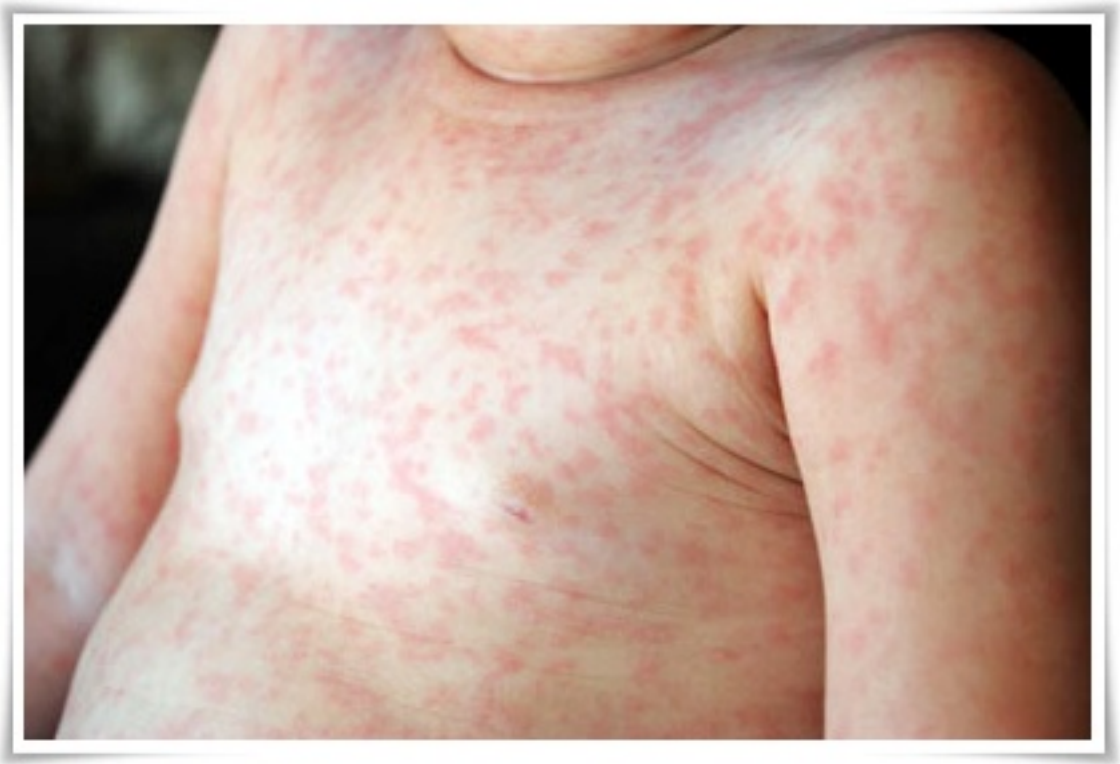
- These homologous regions may be:
  a) contamination in 2nd generation sequencing data;
  b) human genes in viruses;
  c) viral genes in human genome
    - endogeneous retrovirus integrations
    - HIV integration in HIV positive individuals
    - papillomavirus integrations in cervical cancer
    - Epstein-Barr virus integration during the immotalization of cell cultures

Can viruses integrate into genomes of **germ line** cells and this way make phenotypically important structural changes in the human genome?

Human Herpesvirus Classification

Type	Synonym	Subfamily	Primary Target Cell	Pathophysiology	Site of Latency	Means of Spread
HHV-1	Herpes simplex virus-1 (HSV-1)	α (Alpha)	Mucoepithelial	Oral and/or genital herpes (predominantly orofacial), as well as other herpes simplex infections	Neuron	Close contact (oral or sexually transmitted infection)
HHV-2	Herpes simplex virus-2 (HSV-2)	α	Mucoepithelial	Oral and/or genital herpes (predominantly genital), as well as other herpes simplex infections	Neuron	Close contact (sexually transmitted disease)
HHV-3	Varicella zoster virus (VZV)	α	Mucoepithelial	Chickenpox and shingles	Neuron	Respiratory and close contact (including sexually transmitted disease)
HHV-4	Epstein-Barr virus (EBV), lymphocryptovirus	γ (Gamma)	B cells and epithelial cells	Infectious mononucleosis, Burkitt's lymphoma, CNS lymphoma in AIDS patients, post-transplant lymphoproliferative syndrome (PTLD), nasopharyngeal carcinoma, HIV-associated hairy leukoplakia	B cell	Close contact, transfusions, tissue transplant, and congenital
HHV-5	Cytomegalovirus (CMV)	β (Beta)	Monocyte, lymphocyte, and epithelial cells	Infectious mononucleosis-like syndrome,[17] retinitis, etc.	Monocyte, lymphocyte, and ?	Saliva, urine, breast milk etc
HHV-6A and 6B	Roseolovirus, Herpes lymphotropic virus	β	T cells and ?	*Sixth disease* (roseola infantum or *exanthem subitum*)	T cells and ?	Respiratory and close contact?

Roseola infantum



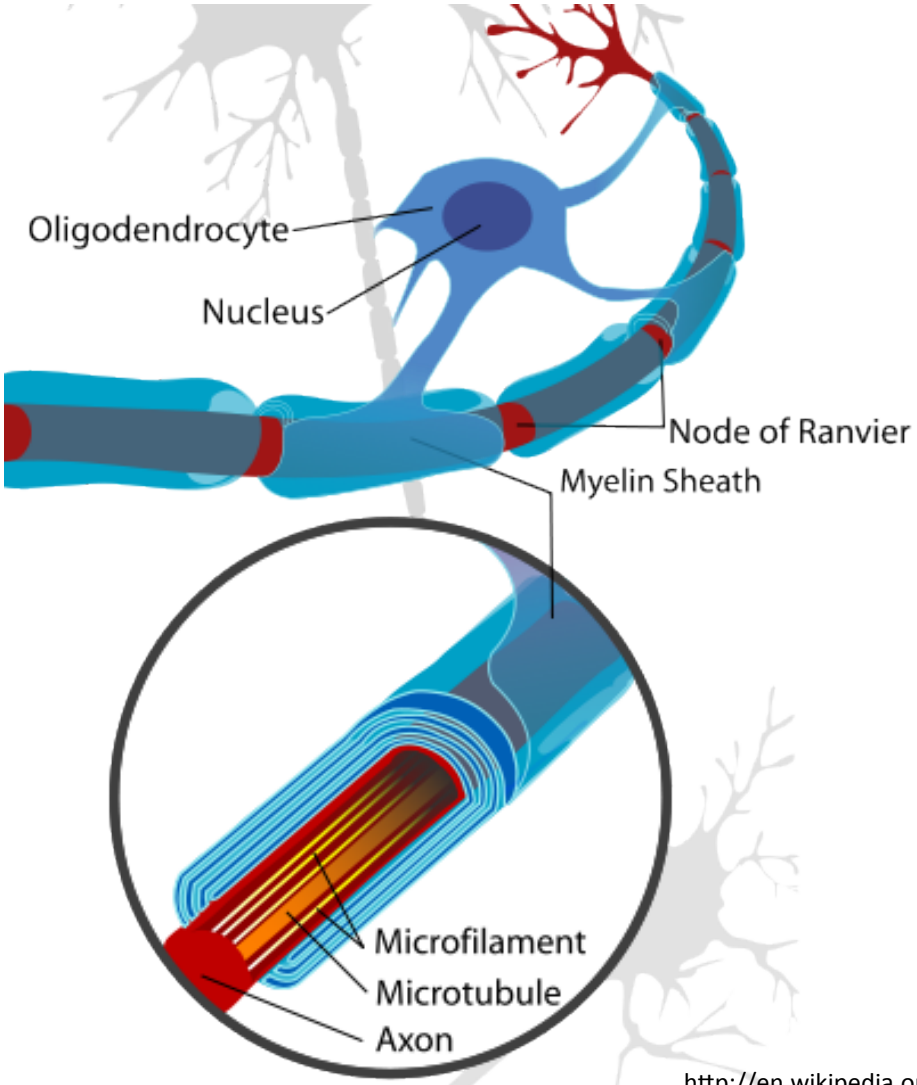
(Lastehaigus, millega kaasneb leetrite või punetiste sarnane lööve)

Human Herpesvirus type 6 (HHV-6)

- HHV-6 is a betaherpesvirus related to the human cytomegalovirus, and there are two distinct subgroups, HHV-6A and HHV-6B. **More than 90% of children experience HHV-6B infection early in life**, and this subtype is the primary cause of exanthem subitum.
- Following primary infection, both variants of HHV-6 remain in a persistent/latent state for the life of the host.

- **HHV-6 has ability to establish latency in oligodendrocytes**.

Neuron with oligodendrocyte



http://en.wikipedia.org/wiki/File:Neuron_with_oligodendrocyte_and_myelin_sheath.svg

Human Herpesvirus type 6 (HHV-6)

- Following primary infection, both variants of HHV-6 remain in a persistent/latent state for the life of the host. However**, the virus may reactivate** in immunocompetent and, more often, in immunosuppressed hosts.
- Reactivation of HHV-6 has been associated with seizures, encephalitis, and graft rejection.

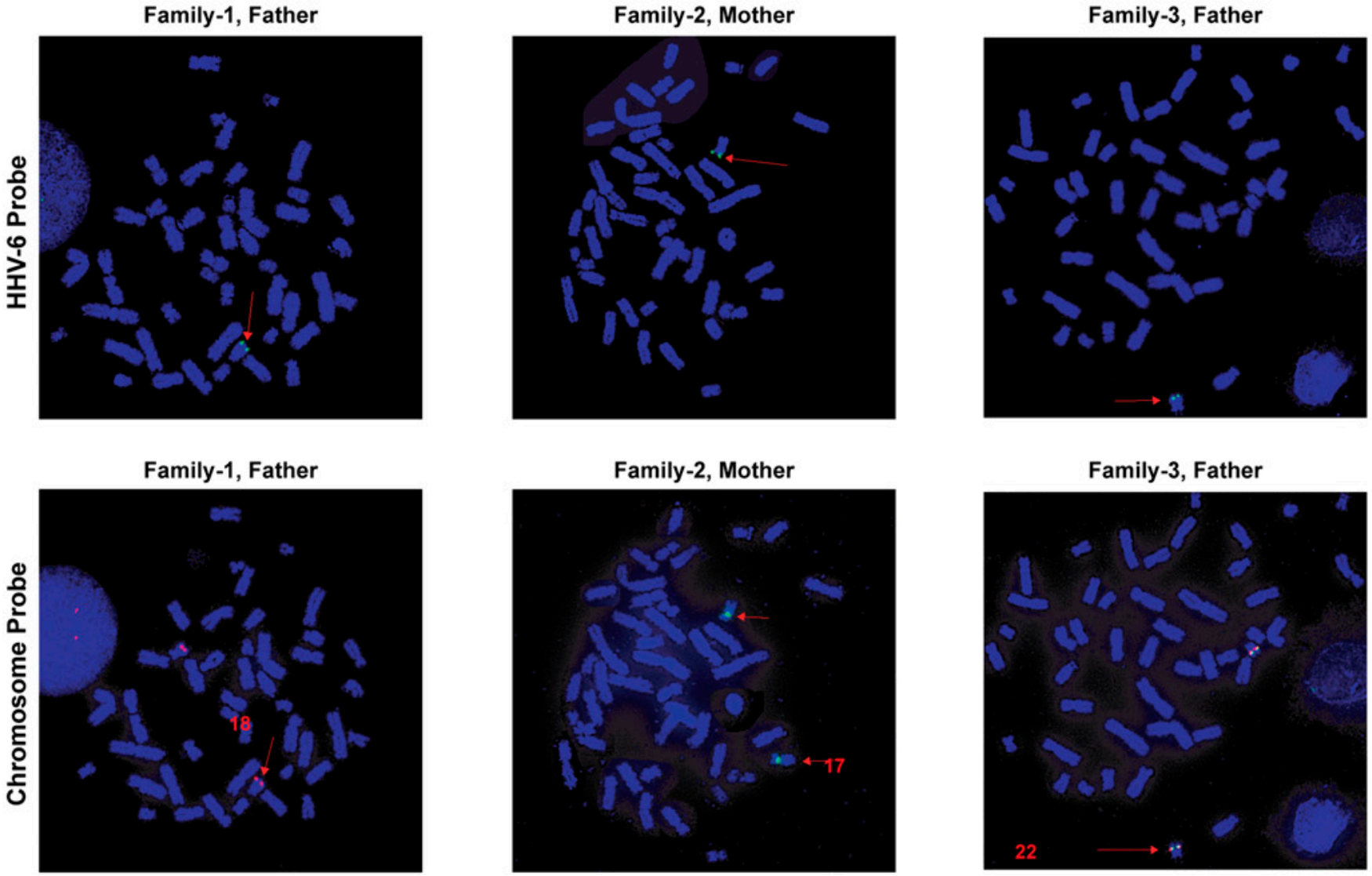
- The prevalence of **high viral load in normal blood donors** has been reported to range from 0.8% to 1.5% (34). Interestingly, an even higher prevalence— 2.9–3.3%—has been reported in hospitalized patients (33).

Table 1. Patients from four independent families with chromosome integrated HHV-6

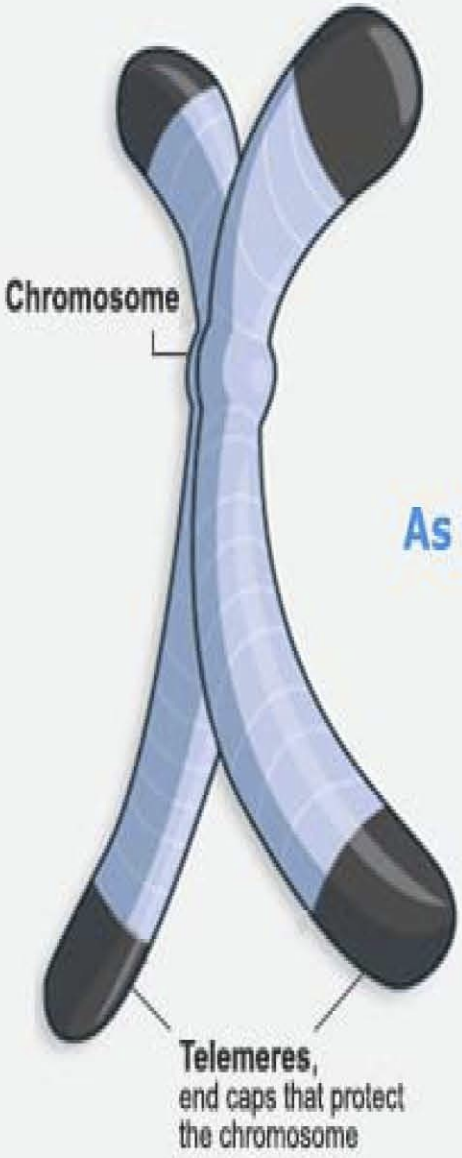
Family number	Age, sex	Subject	Disease stage	HHV-6 qPCR,* copies per mL	HHV-6 subtype†	Chromosome HHV-6 FISH
1	58, M	Father	Asymptomatic	629,000	A	18q23
1	54, F	Mother	PCR negative	Negative	Negative	n/a
1	24, M	Sibling-1	Asymptomatic	1,400,000	A	18q23
1	22, F	Sibling-2	CNS dysfunction, hypersomnia	1,700,000	A	18q23
1	12, M	Sibling-3	CNS dysfunction, ataxia	1,600,000	A	18q23
2	80, F	Mother	Mild dementia	625,000	A	17p13.3
2	45, F	Sibling-1	CNS dysfunction, fatigue	4,100,000	A	17p13.3
3	76, M	Father	Asymptomatic	2,000,000	B	22q13.3
3	61, F	Mother	PCR negative	Negative	Negative	n/a
3	34, M	Sibling-1	CNS dysfunction, fatigue	2,000,000	B	22q13.3
4	62, F	Mother	Asymptomatic	4,000,000	B	Not done
4	36, M	Sibling-1	Asymptomatic	4,500,000	B	Not done
4	29, F	Sibling-2	CNS dysfunction, fatigue, ataxia	4,200,000	B	Not done

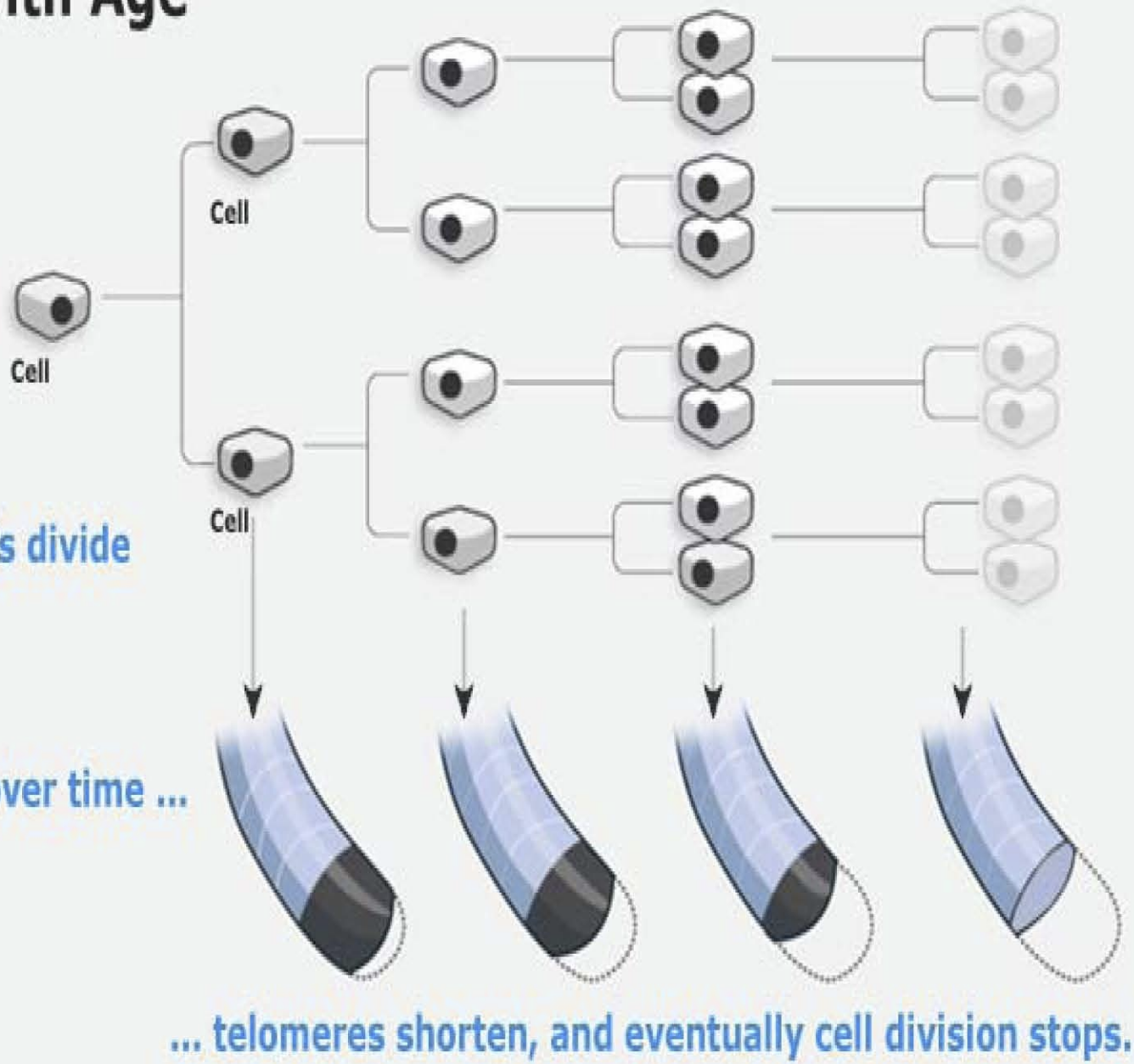
*qPCR on whole blood completed by ViraCor Laboratories (Lee's Summit, MO).
†Subtypes were determined using PCR with subtype-specific primers.

Determination of the Chromosomal Integration Site



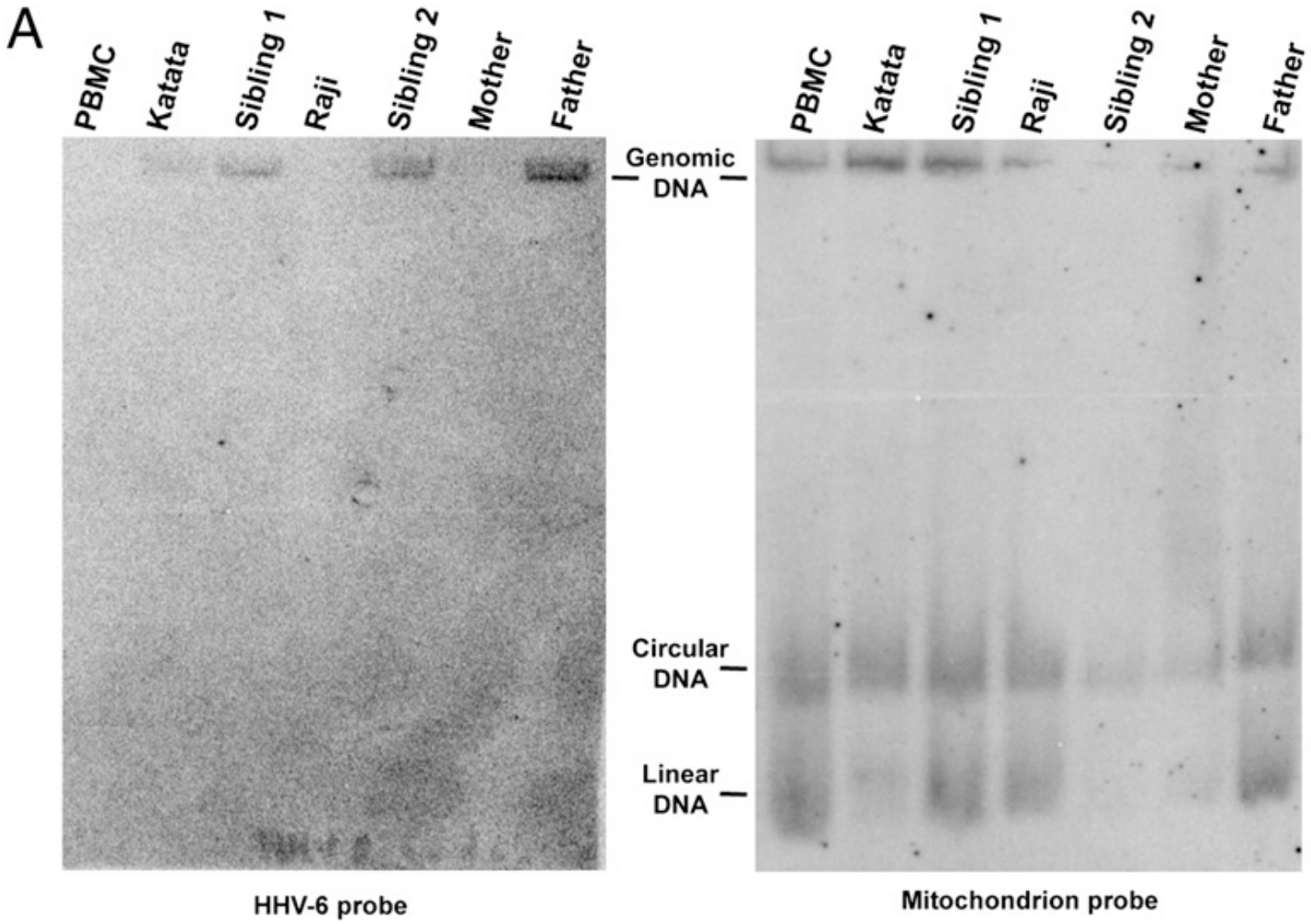
What We Lose With Age





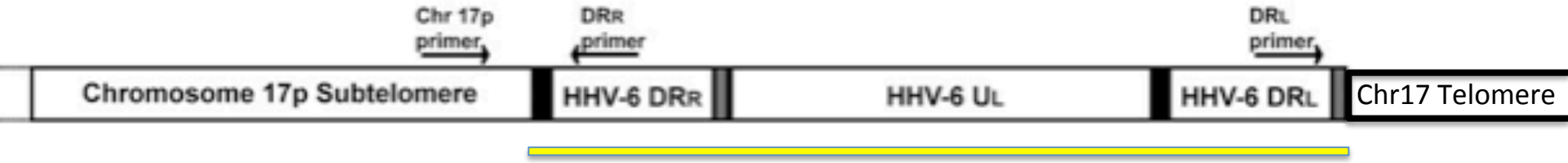
http://www.prweb.com/releases/2011/3/prweb8202989.htm

FISH method truly detects integration of HHV-6 into the human genome, rather than an association of the telomere with episomal viral DNA

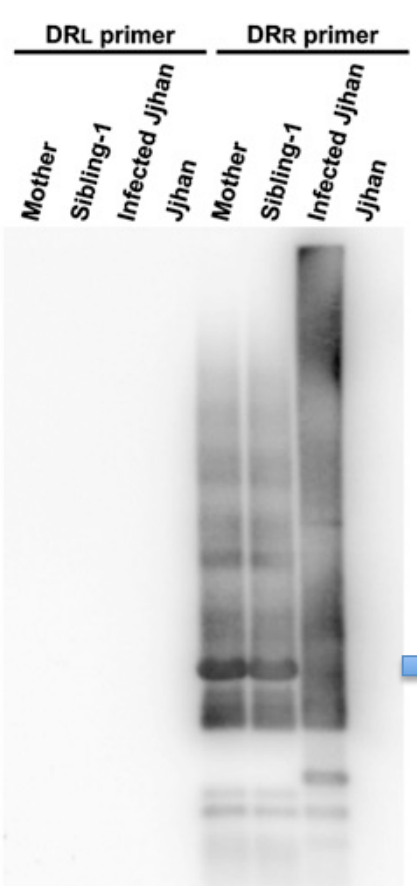


1 million T cells isolated from Family-1, Southern blot

Determination of the Chromosomal Integration Site (by sequencing)



Determination of the Chromosomal Integration Site



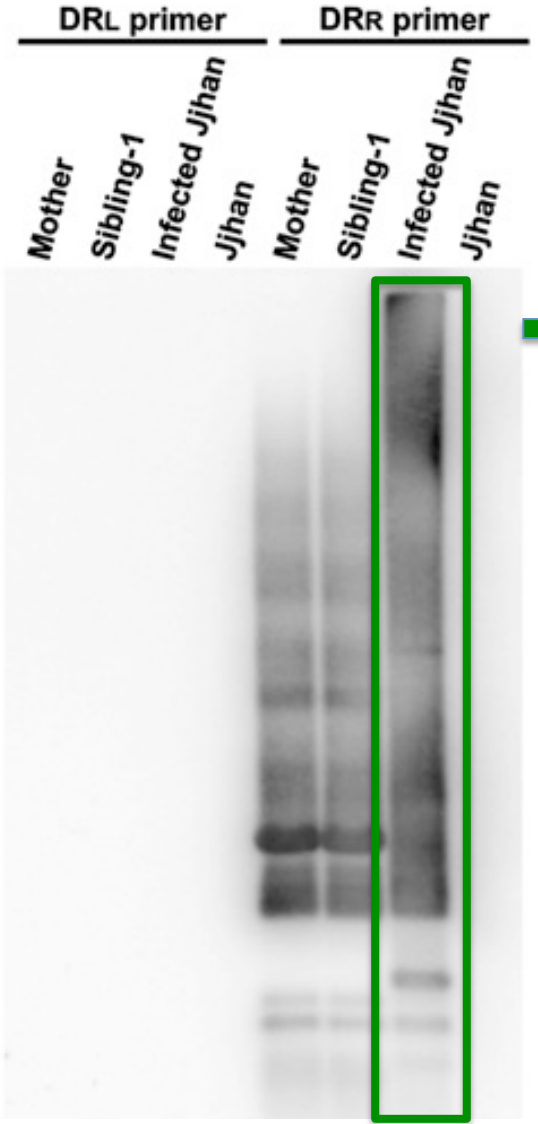
TCGAATCCACGGATTGCTTTGTGTACTTTGGGAAACTTAACA
ATGTGGTCTACAAATCCACAAATAAGATACATTTTTACATTTA
CTGGAAGTTTAATTTCCTTAAGTAATGTCTTATAATTTCCCTC
ATCTAAGTCTTGTCGTTTCATTCCATTTATTCCTAAGTATAATA
TTGCTATTGGTATTGTTTAAGGTAGAATTTTCATAATTTGGTTT
AGAGATTATTCATTCCTAGCATATACATATAAAATGGAATGTTT
GGCTAGGCACCCGGGCTCATACCTGTAACCCAAGCAGGTT
GAGAGGCTGAGGAAGGG**TTAGGGTTAGGGTTAGGGTTAG**
GGTTAGGGTTAGCCGGTGGTTTCCTTTGGCACCGTGCCAG
GCGACCGTCGGTCCCAGACGGTGGCACGTCGCGCGCGAT
GTCGTTTTGAATTGTCTTCAAGTCTCACCCCGGTATGCCCC
ATCTACGTACCCACCCGCGACTACCACATGGGTGGGTTGT
GCGTGTCTGTGTGTCTGCGTGTGTACGCGTCCGTGGTAGA
TACGCGGTGACAACGGATTACGGAGGTGACTGTTGCGTTG
GGTGGGACGGCGAGGGGGTGAAGAGGTGTTTCCCGTATA
GGTGTTTTTGGAACATGGTTTTTTTTCTTATACTTGCCATGCT
AGCGGTCGCCCTCTGTCTTCGGTCCGCGTGACCGTGTCGT
GTGCACTTCCGCATACTTTTGTCTTTGCGCCTCCATACACC
CCGTTGATTGGATGATCGCCACATGTGTATTCGATGTCATAG
TCTGCTATTTTTTTTCACTGTCTATTTTTAAACCTGTTGTCGT
CTTCCCGCCAAGGCTGTGCGTCTCCGCCTTTTATTATTTTTT
TTTACGCTGTTTCTTTTCTACGTTCGCCTCCAACTCCGGAC
GCACCTCCTTTGTATGTCGACTCCTCCCACTCCCTGGGGT
GCCTATATAAGAGACCAACGCGACGCGCTTTCAAGCAGTCC
CGATCTATG

Chromosome 17p

HHV-6 DRR

The integration site contained five TTAGGG repeats, and integration resulted in the loss of 79 nucleotides from the far right end of the viral genome.

HHV6a can integrate *in vitro* during the productive infection.



First, we evaluated whether HHV-6A strain U1102 can integrate into telomeres of the T cell line Jjhan. These cells are routinely used to propagate HHV-6A, yet we observed that despite supporting lytic infection, Jjhan cells often were not lysed and that many cells survived after the peak of productive infection. **We hypothesized that in some of the infected cells, rather than productive infection leading to lysis, the virus had achieved latency through integration.**

Sequencing HHV-6A Jjhan chromosome integration sites

After cloning and sequencing several PCR products, the HHV-6A genome was found to be covalently linked with all chromosomes tested.

>Chromosome 17p integration-clone 2

TAACATCGAATCCACGGAATGCTTGTGTACTTGGAAACTTAACAATGTGGTCTACAAATC
CACAAATAAGATACATTTTTACATTTACTGGAAGTTTAATTCCTAAGTAATGTCTTATAA
TTTCCCTCATCTAAGTCTGTCGTTTCATTCCATTTATTCGTAAGTATAATATTGCTATTG
GTATTGTTTAAGGTAGAATTTTCATAATTTGGTGTAGAGATTATTCATTCCTAGCATATA
CATATAAAATGGAATGTTTGGCCAGGCACCCGGGCTCATACCTGTAACCCAAGCAGGTTG
AGAGGCTGAGGAAGGG**TTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGG**TTAGCCGG
TGGTTTCCTTTGGCACCGTGCCAGGCGACCGTGGGTCCCAGACGGTGGCACGTCGCGCGC
GATGTCGTTTTGAATTGTCTTCACGTCTCACCCCGGTATGCCCCATCTACGTACCCACCC
GCGACTACCACATGGGTGGGTTGTGCGTGTCTGTGTGTCTGCGTGTGTACGCGTCCGTGG
TAGAAACGCGGTGACAACGGATTACGGAGGTGAATGTTGCGGTGGTTGGGACGGGGAGGG
AGTGAAGAGATGTTTCCCGTATAGGTGTTTTGGAACGTGGTTTTTTTTTTCTTACACTGC
CATGCTAGCGATCGCCCTCTGTCTTCGGTCCGCGTTACCGTGTCGTGTGTACTTCCGCAT
ACTTTTGTCTTGCGCCTCGATACACCCCGTTGATTAGATGATCGCCACATGTGTATTGGA
CGTCACAGTCTGCTATTTTTTTCACTGTCTATTTTTAAACCTGTTGTCGTCTTCCCGCCA
AGGCTATGTGTCTCCGCCTTTTCTATATTTTTCTGACGCTGTTCGTTTTCTACGTTCGCC
TCCAATCCCGGACGCACCTCCTTTGTATGTTCACTCCTCCCACCCCCCGGGGTGCCTATA
TAAGAAGCGAACGCGACGCGCTTTCAAGCAGTCCCGATC

Chromosome 17p

Telomere

HHV-6 DR_R

Sequencing HHV-6A
Jjhan chromosome integration

>Chromosome 11q integration-clone 3

CAGACCTTGGAGGCACGGCCTTCGTTTGGGACAATTCGGGGCCGCATCGACGGTGAATAA
AATCCTTCCTCTTTGCAGCCCTGAATAATCAGGGTCAGAGATCAG**TTAGGGTTAGGGTTA**
GGGTTAGGGTTGGGGTTGGGGTTGGGGTTGGGGTTGGGGTTAGGGTTAGGGTTAGGGTTA
GGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTA
GGGTTAGGGTTAGCCGGTGGTTTCCTTTGGCACCGTGCCAGGCGACCGTGGGTCCCAGAC
GGTGGCACGTCGCGCGCGATGTCGTTTTGAATTGTCTTCACGTCTCACCCCGGTATGCCC
CATCTACGTACCCACCCGCGACTACCACATGGGTGGGTTGTGCGTGTCTGTGTGTCTGCG
TGTGTACGCGTCCGTGGTAGAAACGCGGTGACAACGGATTACGGAGGTGAATGTTGCGGT
GGTTGGGACGGGGAGGGAGTGAAGAGATGTTTCCCGTATAGGTGTTTTTGGAACGTGGTT
TTTTTTTCTTACACTTGCCATGCTAGCGATCGCCCTCTGTCTTCGGTCCGCGTTACCGTG
TCGTGTGTACTTCCGCATACTTTTGTCTCTGCGCCTCGATACACCCCGTTGATTGGATGA
TCGCCACATGTGTATTGGACGTCACAGTCTGCTATTTTTTTCACTGTCTATTTTTAAACC
TGTTGTCGTCTTCCCGCCAAGGCTATGTGTCTCCGCCTTTTCTTATATTTTTCTGACGCT
GTTCGTTTTCTACGTTCGCCTCCAATCCCGGACGCACCTCCTTTGTATGTTCACTCCTCC
CACCCCCCGGGGTGCCTATATAAGAAGCGAACGCGACGCGCTTTCAAGCAGTCCCGATCA
TG

Chromosome 11q

Telomere

HHV-6 DR_R

>Chromosome 11q integration-clone 5

CAGACCTGGAGGCACGGCCTTCGTTTGGGACAATTCGGGGCCGCATCGACGGAATAAAAT
CCTTCCTCTTGCAGCCCTGAATAATCAGGGCCAGAGATCAG**TTAGGGTTAGGGTTAGGGT**
TAGGGTTGGGGTTGGGGTTGGGGTTGGGGTTGGGGTTAGGGTTAGGGGTTAGGGTTAGGG
GTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGGTTAGGGTTAGGGTTAGGGTTAG
GGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAG
GGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGCCGGTG
GTTTCCTTTGGCACCGTGCCAGGCGACCGTGGGTCCCAGACGGTGGCACGTCGCGCGCGA
TGTCGTTTTGAATTGTCTTCACGTCTCACCCCGGTATGCCCCATCTACGTACCCACCCGC
GACTACCACATGGGTGGGTTGTGCGTGTCTGTGTGTCTGCGTGTGTACGCGTCCGTGGTA
GAAACGCGGTGACAACGGATTACGGAGGTGAATGTTGCGGTGGTTGGGACGGGGAGGGAG
TGAAGAGATGTTTCCCGTATAGGTGTTTTTGGAACGTGGTTTTTTTTTTCTTACACTTGC
CATGCTAGCGATCGCCCTCTGTCTTCGGTCCGCGTTACCGTGTCGTGTGTACTTCCGCAT
ACTTTTGTCTCTGCGCCTCGATACACCCCGTTGATTGGATGATCGCCACATGTGTATTGG
ACGTCACAGTCTGCTATTTTTTTCACTGTCTATTTTTAAACCTGTTGTCGTCTTCCCGCC
AAGGCTATGTGTCTCCGCCTTTTCTTATATTTTTCTGACGCTGTTCGTTTTCTACGTTCG
CCTCCAATCCCGGACGCACCTCCTTTGTATGTTCACTCCTCCCACCCCCCGGGGTGCCTA
TATAAGAAGCGAACGCGACGCGCTTTCAAGCAGTCCCGATCATG

Chromosome 11q

Telomere

HHV-6 DR_R

Sequencing HHV-6A Jjhan chromosome integration sites

>Chromosome 18q integration-clone 4

CTCATGTCCTCGGTCTCTTGCCTCGGCAAAGATTAGATTAGGGTTAGGGTTTGGGTTCGGGTC
AGGGTTAGGGTTAGGGGTTGGGGTTAGGGTTCGGGTTAGGGTCAGGGTTTGGG**TTAGGGTTAG**
GGTTA----------
GGGTTAGGGTTAGGGGTTGGGGTTAGGGTTCGGGTTAGGGTCAGGGTTTGGGTTAGGGTTAGG
GTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGCCGGTGGTTTCCTTTGGCACCGTGCCAG
GCGACCGTGGGTCCCAGACGGTGGCACGTCGCGCGCGATGTCGTTTTGAATTGTCTTCACGTC
TCACCCCGGTATGCCCCATCTACGTACCCACCCGCGACTACCACATGGGTGGGTTGTGCGTGT
CTGTGTGTCTGCGTGTGTACGCGTCCGTGGTAGAAACGCGGTGACAACGGATTACGGAGGTGA
ATGTTGCGGTGGTTGGGACGGGGAGGGAGTGAAGAGATGTTTCCCGTATAGGTGTTTTTGGAA
CGTGGTTTTTTTTTCTTACACTTGCCATGCTAGCGATCGCCCTCTGTCTTCGGTCCGCGTTAC
CGTGTCGTGTGTACTTCCGCATACTTTTGTCTCTGCGCCTCGATACACCCCGTTGATTGGATG
ATCGCCACATGTGTATTGGACGTCACAGTCTGCTATTTTTTTCACTGTCTATTTTTAAACCTG
TTGTCGTCTTCCCGCCAAGGCTATGTGTCTCCGCCTTTTCTTATATTTTTCTGACGCTGTTCG
TTTTCTACGTTCGCCTCCAATCCCGGACGCACCTCCTTTGTATGTTCACTCCTCCCACCCCCC
GGGGTGCCTATATAAGAAGCGAACGCGACGCGCTTTCAAGCAGTCCCGATCTATG

>Chromosome 18q integration-clone 5

CTCATGTCCTCGGTCTCTTGCCTCGGCAA**AGATTA**GATTAGGGTTAGGGTTTGGGTTCGGGTC
AGGG**TTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGT----------**
TAGGGTTAGGGTTCGGGTCAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAG
GGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGT
TAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAG
GGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGCCG
GTGGTTTCCTTTGGCACCGTGCCAGGCGACCGTGGGTCCCAGACGGTGGCACGTCGCGCGCGA
TGTCGTTTTGAATTGTCTTCACGTCTCACCCCGGTATGCCCCATCTACGTACCCACCCGCGAC
TACCACATGGGTGGGTTGTGCGTGTCTGTGTGTCTGCGTGTGTACGCGTCCGTGGTAGAAACG
CGGTGACAACGGATTACGGAGGTGAATGTTGCGGTGGTTGGGACGGGGAGGGAGTGAAGAGAT
GTTTCCCGTATAGGTGTTTTTGGAACGTGGTTTTTTTTTCTTACACTTGCCATGCTAGCGATC
GCCCTCTGTCTTCGGTCCGCGTTACCGTGTCGTGTGTACTTCCGCATACTTTTGTCTCTGCGC
CTCGATACACCCCGTTGATTGGATGATCGCCACATGTGTATTGGACGTCACAGTCTGCTATTT
TTTTCACTGTCTATTTTTAAACCTGTTGTCGTCTTCCCGCCAAGGCTATGTGTCTCCGCCTTT
TCTTATATTTTTCTGACGCTGTTCGTTTTCTACGTTCGCCTCCAATCCCGGACGCACCTCCTT
TGTATGTTCACTCCTCCCACCCCCCGGGGTGCCTATATAAGAAGCGAACGCGACGCGCTTTCA
AGCAGTCCCGAT

Chromosome 18q

Telomere

HHV-6 DR_R

Chromosome 18q

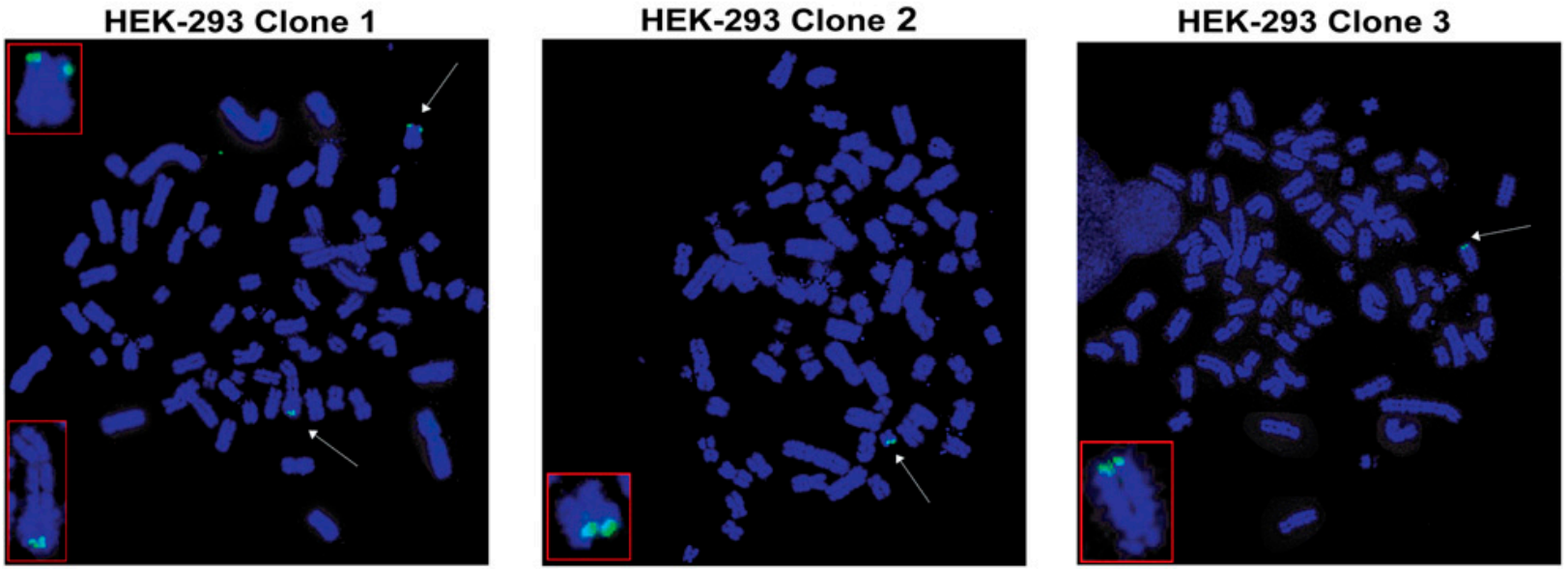
Telomere

HHV-6 DR_R

How frequent is the integration?

We infected HEK-293 cells at 50% confluency with HHV-6A (U1102) at 0.1 multiplicity of infection (MOI). **The cultures were incubated for 5 days**. Then the cells were washed to remove extracellular virus, and single cells were introduced in each well of a 96-well plate. The single cells in each well were then expanded: **10 out of 22 clones were positive for the presence of the viral genome** using ORF U94-specific PCR (Fig. S6A).

Three PCR-positive clones and one PCR-negative clone were studied for integrated HHV-6 by FISH. In two PCR-positive clones, FISH analysis identified integrated HHV-6A in one chromosome. In the third PCR-positive clone, **the virus had integrated into two chromosomes** (Fig. S6B).



Viral episome of HHV-6A is not detectable in HEK-293 cell lines with integrated virus

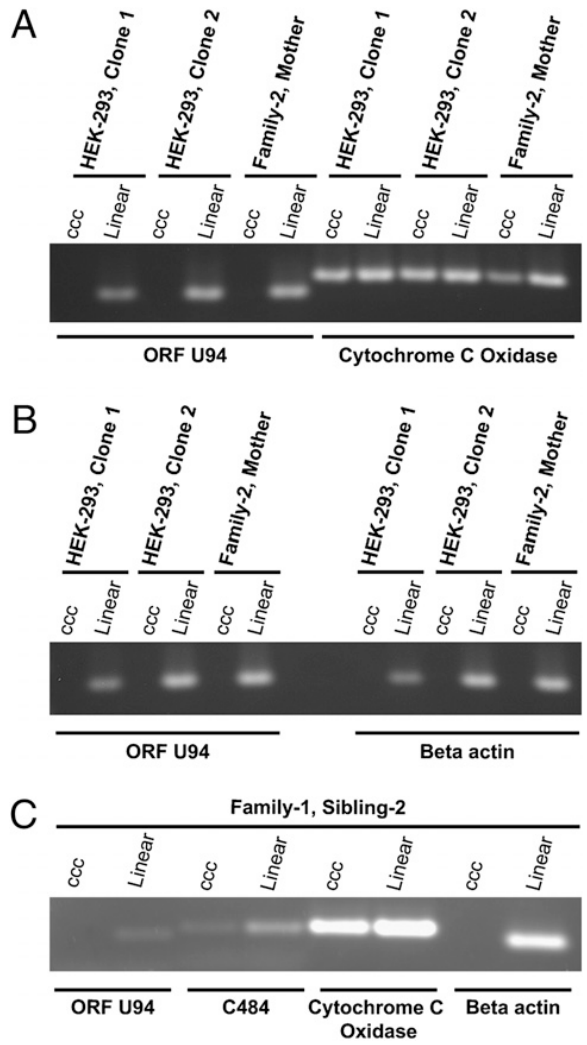


Fig. 3. PCR amplification fails to detect HHV-6 DNA in episomal fractions of CsCl/ethidium bromide (EtBr) gradients. To search for covalently linked circular viral episomes by a method more sensitive than the method of Gardella et al., 50 μg of DNA from two latently infected HEK-293 clones, T cells from Family-2/Mother, and T cells from Family-1/Sibling-2 immortalized with HVS strain C484 were subjected to CsCl/EtBr gradient ultracentrifugation for 2 days (CsCl density 1.55 g/mL, 10 μg/mL EtBr; VTi 65 Rotor at 40,000 rpm). After centrifugation, fractions were collected, and linear and episomal (ccc) DNA was identified by agarose electrophoresis. Salt and EtBr were removed from combined linear and episomal ccc fractions and subjected to PCR based amplification using primers to HHV-6 ORF-U94 and mitochondrial cytochrome *c* oxidase (positive episomal control) (*A*), HHV-6 ORF-U94 and β-actin genomic positive control (*B*), and HHV-6 ORF-U94, C484 Stp, and cytochrome *c* oxidase (positive episomal control) (*C*). ccc, covalently closed circular episomal fraction.

Reactivation of Integrated HHV-6A

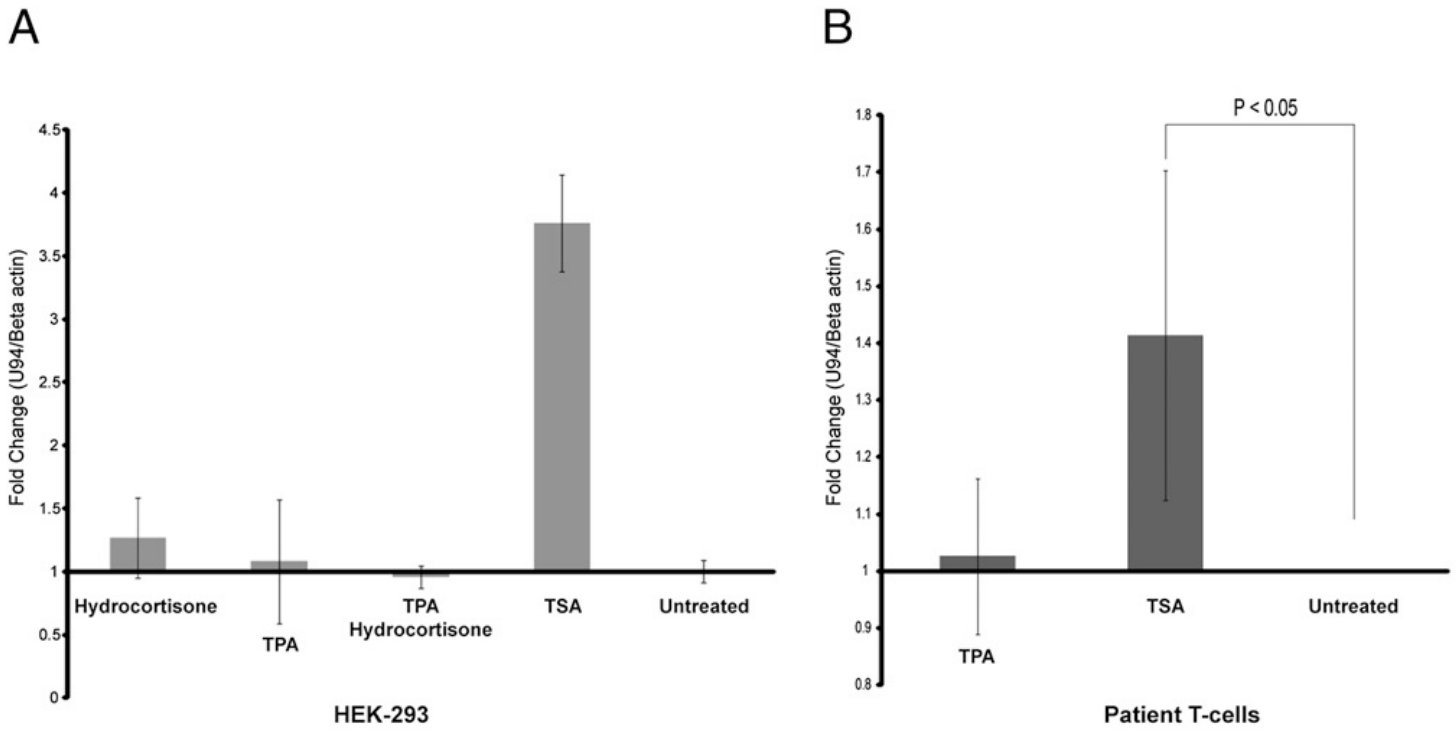


Fig. 4. HHV-6 DNA qPCR analysis of patient T cells and in vitro latently infected HEK-293 cell lines induced by TPA and TSA. T cell cultures from five family members and three latently infected HEK-293 cell lines were treated with known inducers of herpesvirus lytic replication protein kinase-C inducer TPA (20 ng/mL) and histone deacetylase inhibitor trichostatin-A (TSA) (80 ng/mL) for 3 days. (A) HEK-293 cells (n = 3) (Fig. S8). (B) T cells (n = 5) (Fig. S8). **TSA promoted a significant increase in viral DNA replication, whereas the stimulation with TPA and hydrocortisone had a milder effect.**

Infective viruses are generated after reactivation of integrated HHV-6A

To determine whether the increase of viral DNA copy number indicated the production of infectious virus, we isolated PBMCs from six members of **Family-1 and Family-2 whose cells had been cultured in the presence of TPA and hydrocortisone**, leading to a marked increase in copy number.

We **cocultured these cells** with Molt-3 cells in the presence of TPA and hydrocortisone. Syncytia formed in the Molt-3 cells infected with the virus from induced T cells, and replicating linear viral DNA and RNA were detected in these cells by Gardella gel (Fig. 4C and Fig. S9). **Sequencing of the virus in the Molt-3 cells confirmed that it was identical to the integrated sequence in the cells of Family-1 and Family-2** (Fig. S2).

Conclusions

- HHV-6 easily integrates into telomeric region of several human chromosomes
- Integrated copies can be transmitted vertically from parents to offspring
- Integrated virus can reactivate and can produce infectious virions

Examples of human genes in Cytomegalovirus

Brian P. McSharry,1,2 Selmir Avdic,1,2 and Barry Slobedman1,2*
Human Cytomegalovirus Encoded Homologs of Cytokines, Chemokines and their Receptors: Roles in Immunomodulation.
Viruses. 2012 November; 4(11): 2448–2470.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3509658/

- CMV IL-10
  (75 amino acids which shares 27% amino acid identity with hIL-10)
- Cytokine TNF receptor homolog
- Chemokine CXC and chemokine CC homologs

Table 1. Human cytomegalovirus encoded cytokines, chemokines and their receptors.

Gene name	Homology	Function(s)	Reference(s)
UL21.5	Soluble chemokine receptor	Binds CCL5 preventing host cell signaling	*109*
US27	Chemokine receptor	Role in extracellular spread of virus	*102*
US28	Chemokine receptor	Potential oncogene Promotes chemotaxis Potential chemokine sink	*96-99* *77* *91-93*
UL33	Chemokine receptor	Modulates CXCR4 and CCL5 activity Modulates pUS28 activity	*108* *104*
UL78	Chemokine receptor	Modulates CXCR4 and CCL5 activity Modulates pUS28 activity	*108* *104*
UL111A (cmvIL-10)	Cytokine	Inhibits myeloid cell functions Stimulates B cell proliferation	*10-17* *18*
UL111A (LAcmvIL-10)	Cytokine	Inhibits MHC class II expression	*22*
UL128	Chemokine	Promotes PBMC migration	*50*
UL144	Cytokine receptor	Inhibits T-cell proliferation via BTLA-4 Induces CCL22 via NF-KB	*38* *37, 41*
UL146	Chemokine	Promotes neutrophil chemotaxis	*44*
UL147	Chemokine	Unknown function	