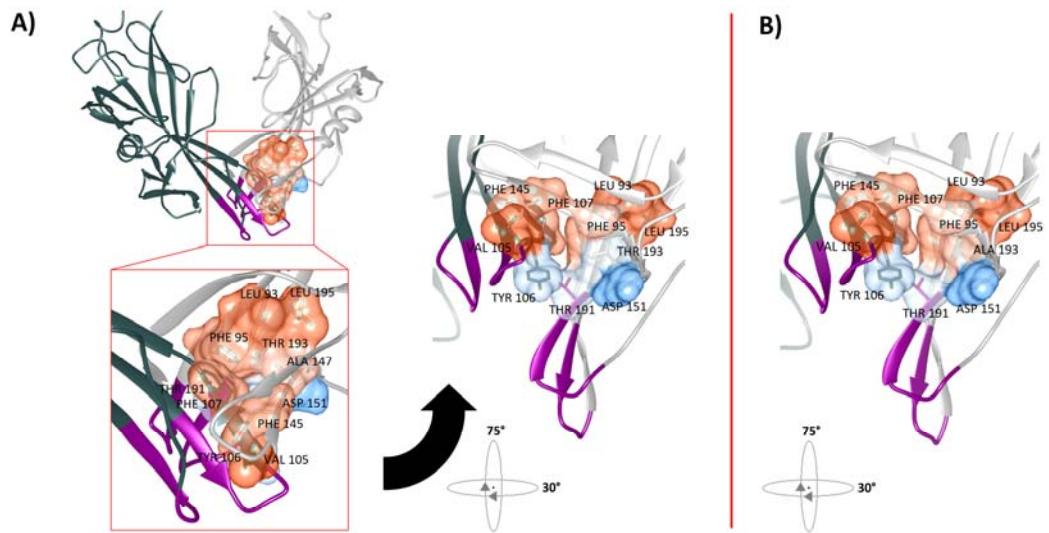


Supplement figures Tweedy et al 2017.

HHV6A	38	<u>FRICSIAKGTDLMRFDRDISCSPYKS-NAKMSEGFFIIYKTNIETYTFPVRTYKKELTFQ</u>	96
		+R+CS+A+GTDL+RF+R+I C+ K N + EG ++YK NI +TF VR Y+K LTF+	
HCMV	91	YRVCSMAQGTDLIRFERNIVCTSMKPINEDLDEGIMVVYKRNIWAHTFKVRVYQKVLTFR	150
		FL1	
HHV6A	97	<u>SSYRDVGVVYFLDRTVMGLAMPVYEANLVNSHAQCYSAVAMKRPDGTVFSAFHEDNNKNN</u>	156
		SY + Y L +A P++E + +NSH+QCYS+ + GTVF A+H D+ +N	
HCMV	151	<u>RSYAYIHHTTYLLGSNTTEYVAPPMEIHHINSHSQCYSSYSR-VIAGTVFVAYHRDSYENK</u>	209
		FL2 Thr193Ala	
HHV6A	157	<u>TLNLFPPLNFKSITNKRFITTKEPYFARGPLWLYSTSLNC1VTEATAKAKYPFSYFALT</u>	216
		T+ L P ++ + + R++T K+ + +RG WLY + +LNC+VT TA++KYP+ +FA +	
HCMV	210	TMQLMPDDYSNTHSTRYVTVKDQWHSRG <u>STWL</u> YRET CNLNCMVTITTARSKYPYHFFATS	269
HHV6A	217	<u>TGEIVEGSPFFNGSN--GKHFAEPLEKLITLENYTMIEDLMNGMNGATTLVRKIAFLEKA</u>	274
		TG++V SPF+NG+N +F E +K I NYT++ D N A R +AFLE+A	
HCMV	270	<u>TGDVVDISPFYNGTNRNASYFGENADKFFIFPNYTIVSDFG-RPNSALETHRLVAFLERA</u>	328
HHV6A	275	<u>DTLF SWEIKEENESVCMLKHWT TVTHGLRAETNETYHFISKE LAAVAPKESLNLTDPK</u>	394
		D++ SW+I++E C L W +R+E ++YHF S ++TA F++ K+ +N++D	
HCMV	329	<u>DSVISWDIQDEKNVT CQLTFWEASERTIRSEAEDSYHFSSAKMTATFLSKQEVNMSDSA</u>	388
HHV6A	395	<u>QTCIKNEFEKIINEVYMSDYNDTYSMNGSYQIFKTTGDLILIWQPLVQKSLMFLEQGSEK</u>	394
		C+++E + +++ + YN TY G+ +F+TTG L++ WQ + QKSL+ LE+ + +	
HCMV	389	LDCVRDEAINKLQQIFNTSYNQTYEKYGNVSVFETTGGLVVFWQGIKQKSLVELERLANR	448
HHV6A	395	----I-----RRRDVG DVKS RHDILYVQLQYLYDTLKDYINDALGNLAESWCL	439
		+ R + + +S H+++Y QLQ+ YDTL+ YIN AL +AE+W+ +	
HCMV	449	SSLNLTHNRTRKSTDGNNATHLSNMESVHNLYVAQLQFTYDTLRGYINRALAQIAEAWCV	508
HHV6A	440	DQKRTITMLHELSKIS PSSIVSEVYGRPISAQLHGDVLAISK CIEVNQSSVQLHKSMRVV	499
		DQ+RT+ + ELSKI+PS+I+S +Y +PI+A+ GDVL ++ C+ +NQ+SV++ + M V	
HCMV	509	DQRRTLEVFKELSKINPSAILSAYNKPIAARFMGDVGLGLASCVTINQTSVKVLRDMNVK	568
HHV6A	500	DAKGVRSETMCYNRPLVTFSFVNSTPEVVPGQLGLDNEILLGDHRTEECEIPSTKIFLSG	559
		++ G CY+RP+V F+F NS+ V GQLG DNEILLG+HRTEEC++PS KIF++G	
HCMV	569	ESPG----RCYSRPVVIFNFANSSY-VQYGQLGEDNEILLGNHRTEECQLPSLKIFIAG	622
HHV6A	560	NHAHVYTDYTHTNSTPIEDI 579	
		N A+ Y DY + I	
HCMV	623	NSAYEYVDYLFKRMIDLSSI 642	

Supplement figure 1. Alignment using Clustal of HCMV strain Merlin gB ectodomain region 91-642 with HHV-6A strain U1102 gB region 38-579 showing 228/541(42%) identity and 362/541(65%) similarity (+), with Domain I, fusion domain, region 79-291 underlined, fusion loops FL1 and FL2 in bold, and passage mutation Thr193Ala shaded.

Alignments by meta-method in M-Coffee ((Wallace, I. M.; O ' Sullivan, O.; Higgins, D. G.; Notredame, C. M - Coffee: combining multiple sequence alignment methods with T - Coffee. Nucleic Acids Res. 2006, 34, 1692–1699).



Supplement figure 2. The passage mutation in HHV-6 gB increases interface hydrophobicity affecting subunit interactions. Visualization of the residues at the interface between two subunits HHV-6A gB and residues surrounding the passage mutation site Thr193Ala. Two interacting subunits are in light and dark grey (A) and (B), with fusion loops, FL1 (residues 100-105) and FL2 (residues 184-191). The lateral chains for the residues 193, 93, 95, 145, 147, 151, 191, 195, 105, 106 and 107 located in the interface or near the position 193 were displayed (The residues 193, 93, 95, 145, 147, 151, 191 and 195 in one subunit and the residues 105, 106 and 107 in the other as visualising only one interface). The surfaces displayed correspond to their hydrophobicity (Kyte-Doolittle scale), blue hydrophilic to white at 0.0 to red hydrophobic. In (A) a global view of the interface between the Domains I of two subunits is shown (Top-left image) focusing on the subunit interfaces (Bottom left). The two other images in (A) correspond to a left-side view of the image located in bottom-left (Bottom-right image) and a top-view of the image in bottom right (Top-right image). The two images in (B) correspond to the same views with the passage substitution Thr193Ala. Stability predictions between the two HHV-6A gB subunits show a stabilizing change of the free energy value of 0.056 for a Thr193Ala mutation in one of the subunits. This contributes to the hypothesis that stabilization of subunit-subunit interactions from mutation of Thr193 to the Ala residue acts via increasing the hydrophobicity of the hydrophobic pocket (Residues 93, 95, 145, 147 and 195 surrounding 193Thr, and all conserved in HCMV as shown above). These are in Domain I where the subunits interact (at the subunits interface; residues 193, 93, 95, 145, 147, 151, 191 and 195 in one face and residues 105, 106 and 107 in the other face).

HHV-6A_U1102
HSV-1_KOS_2gum
HSV-1_KOS_3nwa
EBV_B95-8_3fvc
HCMV_Towne_4osn
HCMV_Towne_5c6t
HCMV_AD169_5cxf

1 51 101 151 201 251 301 351 401 451 501 551 601 651 701 751 801

MSKMAVLFLAVPLMNSVLMYICDPDHYIRAGYNHKYPFRICSIAKGTDLRFDRDISCSPYKSNAKMESEGPFFIYTNTIETYTFPVRTYKKELTFQSSYRDVG
-----AN YVCPPTGATDVMQFEDPQRCPCTRPEQNYTEGIAVVFKEENIAPYKFKAUTYKDVTVSQVFGR
DIK-----AENTTADNFYVCPPPTGATVQFEQFRRCPCTRPEQNYTEGIAVVFKEENIAPYKFKAUTYKDVTVSQVFGR
-----QOTSPFPRVCLESSHGDLFRFSSDIQCPSP-----ENHTBGLLMVFKDNIIPIYSPKVRSVTKIVNLLIVNGHR
-----KTPYRVCMSAQCTDLIRFERNIVCT-----SMLDEGIMVVVKRNIVAHTPKVRVYQKVLTFRSSAYHR
-----T-----KTPYRVCMSAQCTDLIRFERNIICTS---MKLDGIMVVVKRNIVAHTPKVRVYQKVLTFRSSAYHR

151 201 251 301 351 401 451 501 551 601 651 701 751 801

VVYFLDRTVMGLAMPVYE---NLVNSHAQCYSAVAMKRFDGTFSAFIEEDNNKNNTLNLPPLNPKSITNNKRFITT---KEPYPARGLWLYSTSTSLSNCIVTEATA
YSEQFMGIFPEDRAPVPFEVIDKINAKGVCRSTAKVNR-NNLTTAFAPIRDHETD-MELKPANAATRTRSGWHTT-DLKYNPNSRVEAPHYGTTVNCIVEEVDA
YSEQFMGIFPEDRAPVPFEVIDKINAKGVCRSTAKVNR-NNLTTAFAPIRDHETD-MELKPANAATRTRSGWHTT-DLKYNPNSRVEAPHYGTTVNCIVEEVDA
ADSVNRRHEEKPSVDSGET---QDMDTTYQCYNAVKMTK-DCLTRVYVDRDGW-NITVNLKPTGGLANGVRYVAQTELVDAPGRVEATYTRITVNCILITDMA
TTYLLGSNTSYVAPPMWET---HHINSHSQCYSYSSRVIACTVFWVAYLRSDSYEENKTQMLPDDYT---HSTRVTVV-KDQWHSRN---LTRETSNLNCMVITTA
TTYLLGSNTSYVAPPMWET---HHINSHSQCYSYSSRVIACTVFWVAYLRSDSYEENKTQMLPDDYT---HSTRVTVV-KDQWHSRN---LTRETSNLNCMVITTA

251 301 351 401 451 501 551 601 651 701 751 801

KAKYVPFSYFALTGEIVECGSPFFNGS---NG-KWFAEPLKLTILENTMIEDLNNNM-NGATTIVRKVIAPEKADTLFSEWEIKEENESVCMLKHWITVHGLR
RSVYVYDEFVLATGDFVYMSPFVYRE-ESTEITTYAADEFRKQVDFGYARDL-----APT-----RNLLTTPKFTVADWVPPKR-SVCTMTKQEVDEMILR
RSVYVYDEFVLATGDFVYMSPFVYRE-ESTEITTYAADEFRKQVDFGYARDLTTK-ARATAPT-----RNLLTTPKFTVADWVPPKR-SVCTMTKQEVDEMILR
KSNSPFDFTVTTGTCVTFMSPFVYDGGKNET---FHERADSFSHVRTNNKIVDYNDR-CTNPQ---GER-RFLDKGTTLSKWL-ENRTAYCPLQHQWQFDSTIA
-----G-----CQLTFWEASERTIR
RSKYPYHFATSTGDDVVDLSFPYNGTRNA-SYFGENADKFIFIPNNTIVSDFGR-P-NSALETHRHLAFLERADSVISWSIDQDEKNTCQLTFWEASERTIR
RSKYPYHFATSTGDDVVDLSFPYNGTRNA-SYFGENADKFIFIPNNTIVSDFGR-P-NAAPELTHRLAFLERADSVISWSIDQDEKNTCQLTFWEASERTIR

351 401 451 501 551 601 651 701 751 801

AETNETYHFIKSKELTAAFPVAKPESLNLTDPK-QTCIKNEPEKLINEVYVMSDVNDTYSMNGSVEQIFKTDGLLILINQPLVQKSLMPL---EQGSEKIRRRLRDVG
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SEYGGSPRFSDAISTFTTNTLTYEPLSRVLDLDCIGKDRADAMDRIPARRYNATHIKVQGQYQYANGQFLIAQPLLNSNTLAELYVREHLLREQSRKPPVER
TETGKSIHFTVNTTGFVNTTNTVQKCNKTMHEKVEAVQDRYTKQGEAITYFITSQGLLAWLPLTPRSL-----KS
SEAEDSYHFSAKMTATFLSKKQEVNMSDSA-LDCVRDEAINKLQQIFNTIS-TNGTEKYGNSVSVFTTGLVUVFVQGIKQH-----LSN
SEAEDSYHFSAKMTATFLSKKQEVNMSDSA-LDCVRDEAINKLQQIFNTIS-TNGTEKYGNSVSVFTTGLVUVFVQGIKQH-----LSN
SEAEDSYHFSAKMTATFLSKKQEVNMSDSA-LDCVRDEAINKLQQIFNTIS-TNGTEKYGNSVSVFTTGLVUVFVQGIKQH-----LSN

451 501 551 601 651 701 751 801

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-----LVAIQLQFTYDTRLGYINRALAQIAEAWCVDQRTTLEVFKELESKINPSAILSAYNKPIAARFMGDVGLASCVTINQTSVKVLRDMNVKESPCR--

501 551 601 651 701 751 801

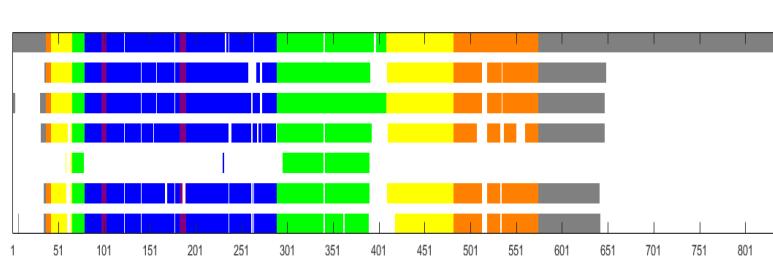
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-----CYSPRLVSPRFEDQGP-LVEQGLQENNELRLLTRDAIPECTVCHRRYFTFGGGVYEEYAYSHQSLRADITTVSTFIDLNITMLEDHEFPVLEVYTRHEI
-----CYSPRLVSPRFEDQGP-LVEQGLQENNELRLLTRDAIPECTVCHRRYFTFGGGVYEEYAYSHQSLRADITTVSTFIDLNITMLEDHEFPVLEVYTRHEI
-----CYSPRLVSPSFSTKTY---EQGLQDTNEIPAT-----SCQYFQSNEIHVNDYHHTKETLQF1SINTSLIENIDFASLELYRDEQ
-----CYSPRLVSPFIPNFA NSS-YVQYQQLGEDNEILLGNHRTREQQLPSLKLIFIAGNSAYEVVDYLFKRMIDLSSISTVDSMIALDIDPLENTDFRVLELYSQKEL
-----CYSPRLVSPFIPNFA NSS-YVQYQQLGEDNEILLGNHRTREQQLPSLKLIFIAGNSAYEVVDYLFKRMIDLSSISTVDSMIALDIDPLENTDFRVLELYSQKEL
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601 651 701 751 801

SANVFDLENILRENSYKSALYTIKEAKATNTPSYVNGINSFLQGLGAI GTGLGSVISVTACALGDIVGGVVSFLKNPFGGLMLILAIVVVVVIIIVVFVRQ
KDSGGLDYTEVQRNRQLHDLRFADIDTVH-----
KDSGGLDYTEVQRNRQLHDLRFADIDTVH-----
RASNVPFLEGIPREYFNQQNIAGLKDLD-----
RSSNVFDLEEIMREFNSYKQRVKY-----
RSSNVFDLEEIMREFNSYKQRVKY-----

701 751 801

RHVLSKP#IDMMMPYATNPVTTVSSVTGTTVVKTPSVKDVDGGTSVAVSEKEEGMADVSQVSDDEYSQEDALKMLKAISLDESYRKPSSESASHASKPSLID



Supplement figure 3. Multiple sequence alignment of sequence of HHV-6A gB with model templates from HCMV, HSV and EBV. The colours correspond to domains I, II, III and IV with fusion loops in purple, as modelled in this study. Summary diagram showing the portions of sequences covered by the different template models (PDB ID : 2gum; 3nwa; 3fvc; 4osn; 5c6t and 5cxf) using meta-method for assembling multiple sequence alignments M-Coffee. (Wallace, I. M.; O'Sullivan, O.; Higgins, D. G.; Notredame, C. M-Coffee: combining multiple sequence alignment methods with T-Coffee. Nucleic Acids Res. 2006, 34, 1692–1699.)