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Abstract

Coxsackievirus A6 (CV-A6) infection is a major etiologic agent for hand, foot and mouth disease (HFMD) in recent years. HFMD outbreaks associated with CV-A6 results from the evolutionary dynamics of CV-A6 and the appearance of novel recombinant forms (RFs). To examine this, 151 variants collected between 2013 and 2014 from Germany, Spain, Sweden, Denmark, and Thailand were genotyped for the VP1 capsid and 3Dpol genes. Analysis of the VP1 gene showed an increasing likelihood between CV-A6 genome recombination and sequence divergence (estimated substitution rate of 8.1×10^{-3} substitutions/site/year and RFs half-life of 3.1 years). Bayesian phylogenetic analysis showed that recent recombination groups (RF-E, -F, -H, -J and -K) shared a common ancestor (RF-A). Thirty-nine full-length genomes of different RFs revealed recombination breakpoints between the 2A-2C and the 5' untranslated regions. The emergence of new CV-A6 recombination groups has become widespread in Europe and Asia within the last 8 years.

Human enteroviruses are genetically diverse RNA viruses within the *Enterovirus* genus in the family *Picornaviridae* and are responsible for a wide spectrum of clinical manifestations (Knowles *et al*., 2012). Human enteroviruses are divided into four species (A to D). Species A, of which coxackievirus A6 (CV-A6) is a member, currently comprises 20 types (Pons-Salort *et al.*, 2015). CV-A6 possesses a positive-stranded RNA genome of approximately ~7,400 nucleotides encapsidated by a highly structured icosahedral capsid. The viral genome is translated into a large polyprotein that is subsequently cleaved into structural (VP1 to VP4) and non-structural (2A to 2C and 3A to 3D) proteins (Whitton *et al.*, 2005). The degree of similarity of nucleotides and amino acid sequences of the VP1 region provides the primary tool for the identification and assignment of new types within a species, in which novel variants showing less than 75% nucleotide sequence identity are classified as new types (Oberste *et al.*, 1999).

CV-A6 infections are typically mild and asymptomatic, whereas enterovirus 71 (EV-A71) and coxackievirus A16 (CV-A16) are most often implicated in causing hand, foot and mouth disease (HFMD), a disease characterized by vesicular exanthema on the hands, feet, and oral mucosa (Puenpa *et al.*, 2011; Schuffenecker *et al.*, 2011; Wu *et al.*, 2010). In 2014, atypical HFMD was linked to CV-A6 infection in children with erythematous papular rash resembling eczema herpeticum (Sinclair *et al.*, 2014) as a result of newly emerging variants of CV-A6. Such novel recombinant forms (RFs) of the virus have been assigned into RF-A to -H based on the 3D polymerase (3Dpol) phylogeny (Gaunt *et al*., 2015; McWilliam Leitch *et al*., 2011). It was subsequently determined that RF-H, which possessed phylogenetically distinct 3Dpol region sequences likely acquired from other human enterovirus species A serotypes through recombination, was largely responsible for the clinically unusual HFMD in Edinburgh, U.K (Gaunt *et al.*, 2015). Here, we further defined how recently emerged RFs

including RF-H and its predecessor RF-A are circulating more widely and contributing to the increased incidence of HFMD elsewhere around the world.

We initially examined the VP1 sequence divergence and 3Dpol sequence grouping by analyzing 151 CV-A6 strains from Denmark (n = 22), Germany (n = 4), Spain (n = 14), Sweden (n = 6) and Thailand (n = 105) collected between 2013 and 2014 (Table S1). Nested RT-PCR was performed using newly designed primers to amplify the VP1 and 3Dpol genes (Table S2), followed by sequencing. The reverse transcription and first-round PCR utilized Superscript III One-Step RT-PCR system with Platinum Taq High Fidelity (Invitrogen), while the second-round PCR utilized GoTaq DNA polymerase (Promega). Sequences were analyzed using the SSE 1.2 sequence editor package (www.virus-evolution.org) (Simmonds, 2012) and phylogenetic tree reconstruction was performed with the MEGA program (v6) using the best-fit models and the maximum-likelihood method (Tamura *et al.*, 2013). All newly generated sequences were deposited in the GenBank database under the accession numbers KX212338 - KX212678.

The VP1 sequences from the CV-A6 identified in Denmark and Spain clustered within lineage I, the very same group of CV-A6 responsible for eczema herpeticum in Edinburgh in 2014 (Fig. S1). They were distinct from CV-A6 from Taiwan (lineage II), Thailand (lineage III), China (lineage IV) and Finland (lineage V). Examination of the sequences from the 3Dpol region enabled the designation of bootstrap-supported clades comprising groups A, B, C, D, E, F, G, H, I, J and K (Fig. 1 and Table S3) in agreement with previous analysis (McWilliam Leitch *et al.*, 2009; McWilliam Leitch *et al.*, 2012; McWilliam Leitch *et al.*, 2010). The majority of the CV-A6 strains clustered within two of the previously assigned recombinant forms RF-A (105/151) and RF-F (37/151). Meanwhile, four variants from Denmark grouped with RF-H, as did two variants from Spain. Additional three variants from Denmark and Spain comprised RF-G.

Strong evidence of recombination was demonstrated by the observed differences in the phylogenetic trees based on the 3Dpol region, for which RF groups were assigned, and VP1 region for several strains. For example, the TW/00141/E/2007 strain was assigned RF-E by the 3Dpol phylogeny, but grouped with the two RF-B strains (FI/TS3FinTu81042/B/2008 and JP/Kyoto1/B/1999) in the VP1 tree. The 3Dpol-assigned RF-J strain CN/P143/J/2013 grouped with some of the RF-A strains. Finally, the CN/CC13/K/2013 is an RF-K strain, but instead appeared next to an RF-D strain CN/HN421/D/2011 in the VP1 phylogeny.

To enable examination of the sequence relationships in other parts of the genome, we obtained 39 nearly complete genome sequences of CV-A6 variants (Germany = 3, Spain = 3, Denmark = 8, Thailand = 25) representing RF-A (n = 21), RF-F (n = 10), RF-G (n = 2), and RF-H (n = 6). Comparison of the phylogenetic trees of the VP1, 5´UTR and VP4/2 regions yielded broadly similar groupings of CV-A6 variants (Figs. 1 and S2). However, several instances of discordance in the trees provided additional evidence for potential CV-A6 recombination. For example, RF-E variants grouped with RF-A and -H in the VP1 but not in the 5´UTR and VP4/2 regions. RF-A strains were interspersed in the 5´UTR and VP4/2 trees with RF-J, which contrasts with their consistent grouping in theVP1 region. All of RF-K was monophyletic in the VP1, VP4/2 and the 5´UTR regions except one which grouped with RF-D. Therefore, the patterns of phylogenetic discordance were consistent with recombination in CV-A6 and in agreement with previous findings for other enteroviruses (Cabrerizo *et al.*, 2014; Calvert *et al.*, 2010; McIntyre *et al.*, 2010; McWilliam Leitch *et al.*, 2009; McWilliam Leitch *et al.*, 2012; McWilliam Leitch *et al.*, 2010).

We estimated the rates of evolution and molecular clock phylogeny (Drummond & Rambaut, 2007) from VP1 gene sequences using the Bayesian Markov Chain Monte Carlo (MCMC) method implemented in BEAST (v1.8.0) (Drummond *et al.*, 2012). Two independent runs involved constant and exponential growth as priors with a chain length of

100 million and a relaxed log-normal molecular clock model were analyzed using the SRD06 model of substitution. All other parameters were optimized during the burn-in period. Convergence of the chains and effective sample sizes of the estimates were checked using Tracer (http://beast.bio.ed.ac.uk/Tracer).

Since sequence divergence in VP1 provides a proxy measure for the time of divergence of CV-A6 variants from which estimates of the life spans of individual recombinant forms can be derived as described previously for echovirus type 30 (E30) isolates (McWilliam Leitch *et al.*, 2009), we evaluated the VP1 evolutionary divergence and the proportion of recombinant comparisons for variants with different 3Dpol groups. Pairwise comparison among CV-A6 variants showed precise correlation between VP1 sequence distances and assignment to different RF group by the 3Dpol region (Fig. S3). Furthermore, an estimate of the approximate RF half-lives of CV-A6 lineages were calculated by combining the mean sequence divergence in VP1 at the 50% recombination frequency threshold (estimated at 0.05) with the substitution rate in VP1 (8.1×10^{-3} substitutions/site/year) (Table 1). This corresponds to a period of 6.17 years (0.05/0.0081) of divergent evolution, or approximately 3.1 years from a common ancestor. This RF half-life of CV-A6 was very much similar to that estimated previously for E30, although higher than E6 and E9 but lower than EV-71 and E11 (Cabrerizo *et al.*, 2014; McWilliam Leitch *et al.*, 2009; McWilliam Leitch *et al.*, 2012; McWilliam Leitch *et al.*, 2010).

To determine when CV-A6 recombination groups first appeared, we reconstruct the temporal phylogeny from VP1 sequences. Since variability of the VP1 sequence was restricted primarily to synonymous sites, most sequence changes likely occurred through neutral drift. Using molecular clock analysis, we estimated the nucleotide substitution rate and times to the most recent common ancestor (tMRCAs) of different regions and the assignment of 3Dpol clades of the greatest RFs (RF-A and RF-F). The substitution rate of

143 the whole data set of all VP1 sequences was estimated to be 8.1×10^{-3} substitutions/site/year
144 (high-probability distribution [HPD] range, 6.0×10^{-3} to 10.5×10^{-3}). The MRCA of all CV-
145 A6 clusters likely first appeared in 1947 (HPD, 1940 to 1949), while that of RF-A probably
146 emerged in 1999 (HPD, 1995 to 2003). The diversity was low for RF-F as demonstrated by
147 their tight clustering at the top of the tree (Fig. 1 and Table 1), whereas RF-A dispersed into
148 other branches and therefore implied that they possessed higher substitution rate. The
149 number of RF-F variants was only one-third that of RF-A and therefore might have
150 contributed to the bias due to sampling size.

151 To determine more precisely the timescale of recombination events underlying the
152 appearance of each RF, datasets of VP1 gene sequences were further analysed using the
153 Bayesian Markov Chain Monte Carlo (MCMC) method to generate time-correlated
154 phylogeny (Fig. 2). While earlier recombination events could not be reconstructed in any
155 detail due to inadequate sampling of CV-A6 before 2008, variants collected after this date
156 were monophyletic and fell into three further lineages with estimated dates of splitting
157 betweeen 2004 and 2005. The oldest lineage comprised purely of RF-G samples, which first
158 appeared in 2011, and thereafter underwent the recombination event that exchanged the
159 3Dpol region sequences between 2004 and 2011. The other two lineages contained samples
160 belonging to RF-A. One comprised solely of RF-A and persisted for at least 11 years (2005
161 to 2015). The other lineage contains RF-A sequences and samples isolated subsequently,
162 which belonged to other RF groups (E, F, H, J and K). In lineage 1, the oldest variants were
163 those originally described in Asia (Thailand and Japan) before 2012 and then spread into
164 Europe and Asia between 2013 and 2014. Within this lineage, CV-A6 variants belonging to
165 RF-F with the recombination event dated between 2009 and 2012. The most recent group,
166 RF-H, which appeared in 2013, probably recombined between 2011 and 2013. The RFs (F,
167 G, H and K) were monophyletic and likely originated from single recombination events,

unlike RF-E and RF-J which were detected in more than one VP1 lineage. With the exception of RF-F which was isolated from both Europe and Asia, other RFs groups were detected only from Europe or Asia; G and H (Europe), E (Taiwan), J and K (China). Variants within lineage 2 (RF-A) were those detected in the first HFMD outbreak in Finland in 2008 along with variants detected subsequently in Europe and Asia over the following 1 to 5 years.

Having identified the likely time course and direction of the recombination events, divergence scan analyses were performed between the ancestral RF-A sequences with complete genome sequences generated in the current study (RF-F, -G, and -H) and the recombinant forms from previous study (RF-J and RF-K) to identify recombination breakpoints (Fig. S4). The sharp increase in sequence divergence at various points in the P2 region provided evidence for the occurrence of separate, individual recombination events for each RF. The first breakpoint was found at the 2A protein-encoding region around nucleotide position 3500 (RF-G). The next breakpoints were located in 2B and at the border between 2B and 2C regions (RF-F, -J and -H). The last breakpoint of RF-K can be recognized at nucleotide position 5000 and included the 3′ part of the 2C region.

This study reports a detailed, multi-centre investigation of the emergence of an enterovirus serotype associated with epidemics of HFMD. It catalogues the complexity of the evolutionary processes associated with its geographical expansion and the occurrence of a number of recombination events each involving replacement of close to complete non-structural gene blocks at varying times since the founder recombinant form RF-A was first described in 2008 (Osterback *et al.*, 2009). Non-structural (NS) region sequences of most RFs have not been described in association with other species A serotypes including any of the RFs described for EV-A71 (McWilliam Leitch *et al.*, 2012). However, there was some evidence for a limited degree of re-circulation within the recombination pool of NS region sequences; RF-E and RF-K appeared at two different positions in the VP1 phylogenetic tree.

193 Furthermore, a limited degree of sharing of NS regions sequences between different species
194 B serotypes has been documented (Bailly *et al.*, 2009).

195 Phylogenetic reconstruction was used to analyze trait evolution such as temporal and
196 geographical correlates of individual recombination events, which was previously
197 incomplete. The most frequently detected recombinant form, RF-A, showed decades-long
198 circulation and was the ancestor of five separate recombination groups (RF-E, F, H, K and J)
199 that have emerged in the past 5-10 years. The HFMD outbreak in Finland in 2008 was
200 associated with RF-A with the subsequent appearance of this RF across of Europe and Asia
201 between 2013 and 2014. The more recent emergence of RFs originated from descendants of
202 multiple VP1 lineages that have diverged from RF-A variants circulating in Asia (Thailand
203 and Japan) between 2008 and 2010. Enterovirus recombination events can play a significant
204 role in the evolution and breakpoints detected in this study (2A - 2C regions) are well-known
205 recombination hotspots (Lukashev *et al.*, 2005). CV-A6 recombination breakpoints within
206 VP3 and between 5´UTR and VP1 have been detected in the genomes of RF-E variants in
207 Taiwan (Gaunt *et al.*, 2015).

208 In summary, the typical pattern for an RF was its rapid emergence, variable
209 penetrance into the sampled virus population and relatively rapid extinction, within years
210 rather than decades, based on the average recombination half-lives documented for CV-A6
211 and other EV types. These patterns are well-attested in the turnover of RFs of CV-A6.
212 While we remain relatively ignorant of the reasons for RF turnover, whether driven by
213 immunological, host adaptive factors or transmissibility, or alternatively whether it occurs as
214 a consequence of population bottlenecks and replacements without a fitness component,
215 molecular epidemiological studies will be of value in understanding the nature of enterovirus
216 evolution and their clinical outcomes.

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Figure Legends

Figure 1. Phylogenetic analysis of CV-A6 variants in different genome regions. Maximum-likelihood trees of (a) VP1 [positions 2485 and 3816 numbered based on the Gdula prototype strain, GenBank accession number AY421764], (b) 3Dpol [positions 5061 and 6364 numbered based on the Gdula prototype strain, GenBank accession number AY421764] and previously determined reference groups (RF-B, -C, -D, and -E). The optimal substitution models were Kimura two-parameter (K2P) with invariant sites (I) for VP1 and K2P with I and gamma distribution (I-) for 3Dpol. Each sequence is identified by the country of origin, sample code, 3Dpol clade assignment and year of collection. Dot colors indicate the recombination group assignments based on 3Dpol phylogeny. Bars denote the evolutionary distance according to the number of nucleotide substitutions per site. Bootstrap consensus was inferred from 1,000 replicates.

Figure 2. A temporal phylogeny of VP1 sequences of CV-A6 variants in this study and published sequences. Branch colours denote recombination groups in each clade. Two RF-A lineages (1 and 2) are noted.

321 **Table 1.** Rates of sequence change and TMRCAs by MCMC analysis.

RF group and geographic set	RF	*n*[†]	Divergence[*]				*dN/dS*		MCMC (BEAST)			
			Nucleotide		Amino acid				Substitution rate (10^{-3})[#]		tMRCA[‡]	
			VP1	3Dpol	VP1	3Dpol	VP1	3Dpol	VP1	3Dpol	VP1	3Dpol
Whole data set												
All	All	244	0.052	ND	0.014	ND	0.035	ND	8.1 (6.0-10.5)	ND	68.2 (66.2-75.4)	ND
Individual RF group												
All	RF-A	160	0.046	0.047	0.012	0.020	0.036	0.057	10.4 (7.6-13.8)	11.0 (8.2-14.4)	15.9 (12.3-20.4)	12.9 (12.2-14.4)
All	RF-F	36	0.016	0.013	0.010	0.006	0.097	0.055	1.4 (0.03-3.0)	6.5 (3.6-10.2)	17.1 (3.0-42.1)	3.5 (2.7-4.4)

322

323 [*] Mean pairwise *P* distances. ND, not determined.

324 [†] Number of sequences in each set analyzed.

325 [#] Mean value with the HPD interval in parentheses.

326 [‡] Time before the present of the most recent common ancestor

Figure 1

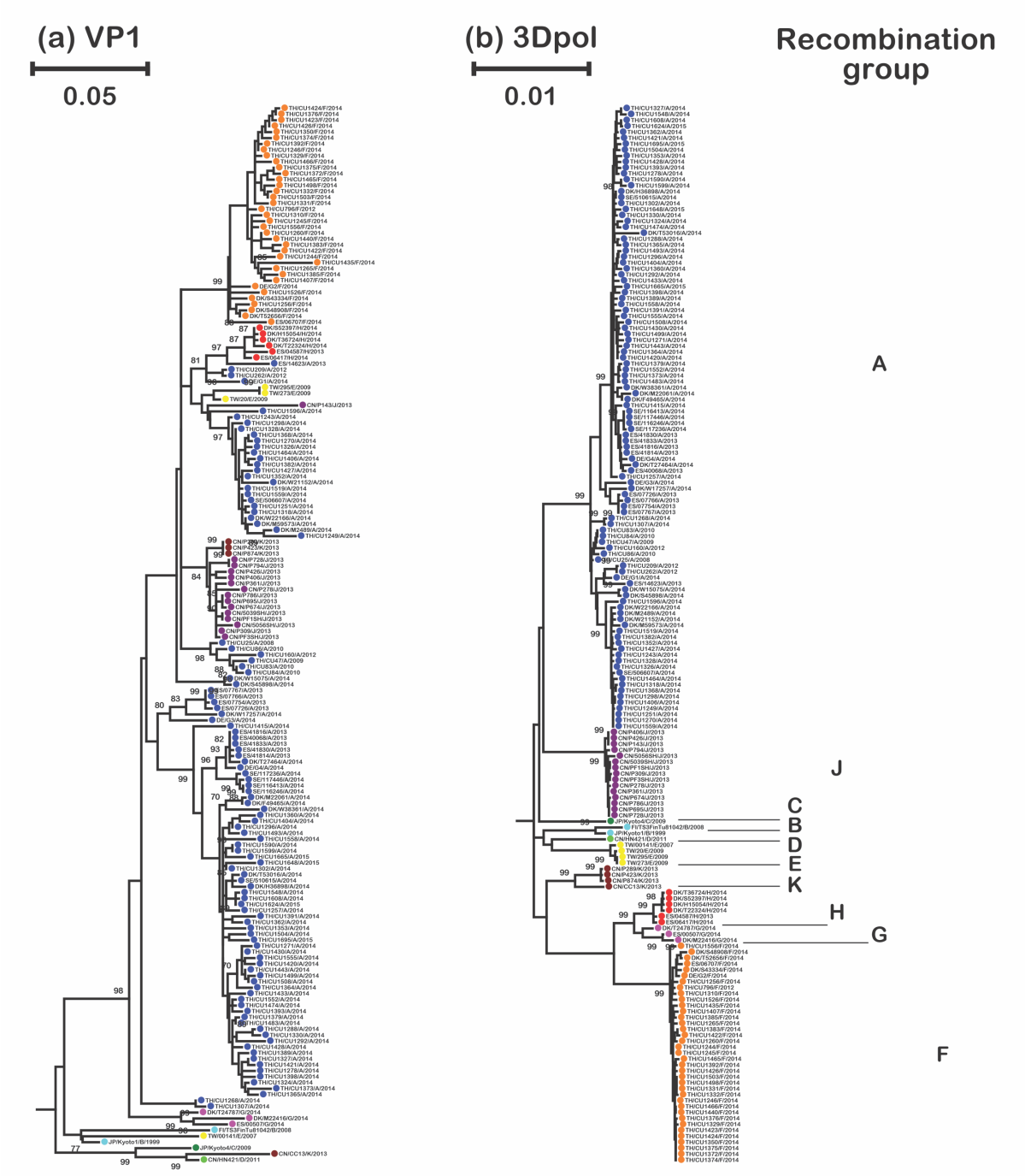
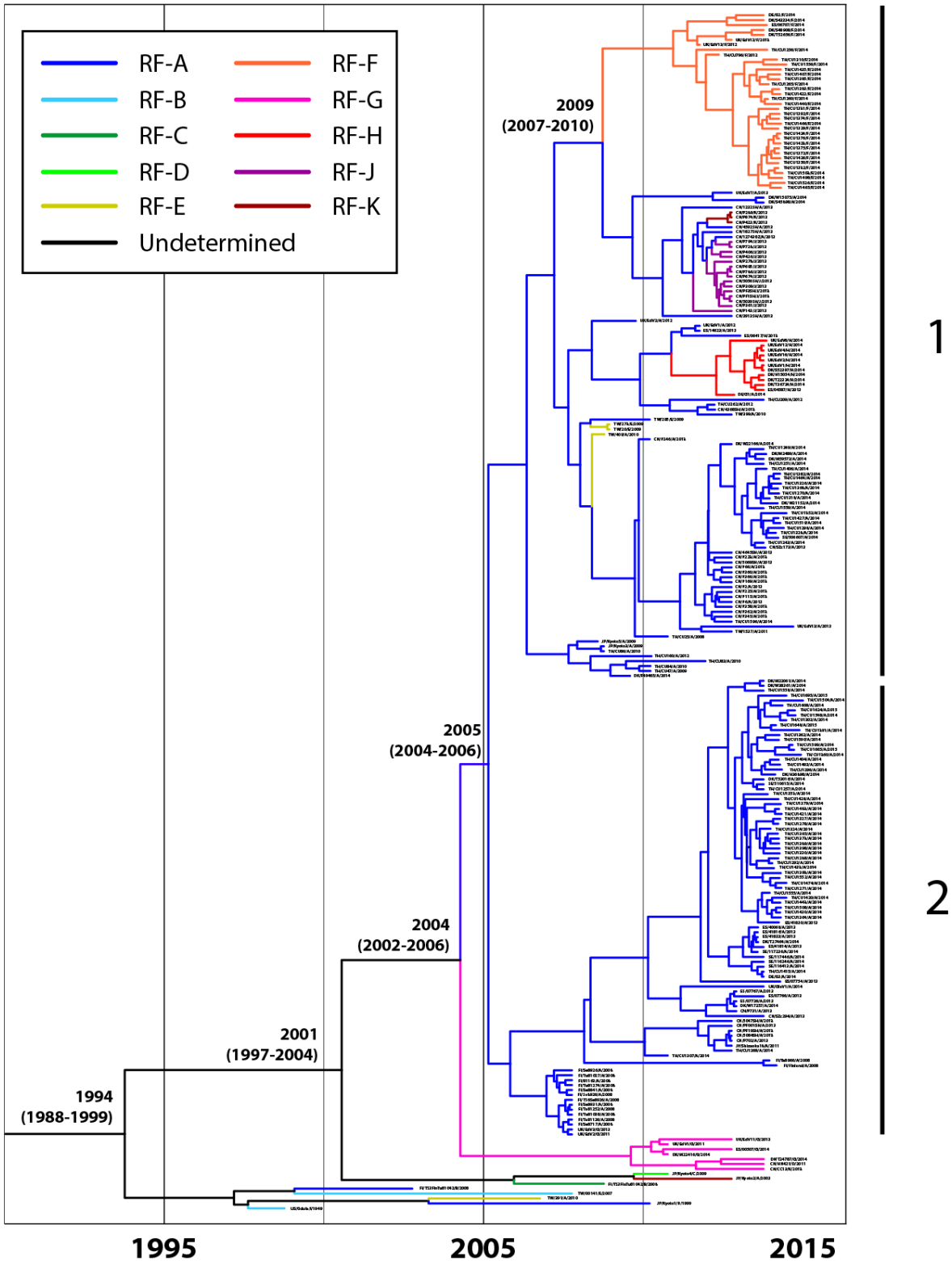


Figure 2


RF-A
RF-B
RF-C
RF-D
RF-E
Undetermined
RF-F
RF-G
RF-H
RF-J
RF-K
2009
(2007-2010)
2005
(2004-2006)
2004
(2002-2006)
2001
(1997-2004)
1994
(1988-1999)
1
2
1995
2005
2015

Supplementary Materials

Supplementary Table S1. Sequence information.

Supplementary Table S2. Primer sets used for whole genome amplification by nested RT-PCR.

Supplementary Table S3. Recombination groups (RF-A to -K) identified in different countries based on phylogenetic analysis of the 3Dpol region**.**

Supplementary Figure S1. Phylogenetic analysis of VP1 nucleotide sequences of CV-A6 for study subjects and those previously determined (RF-B, -C, -D, and -E). Dot colors indicate different countries. Lineages are denoted in Roman numerals.

Supplementary Figure S2. Phylogenetic analysis of CV-A6 variants in different genome regions. Maximum-likelihood trees of (a) 5′UTR [positions 111 and 745 numbered based on the Gdula prototype strain, GenBank accession number AY421764], (b) VP4/2 [positions 746 and 1720 numbered based on the Gdula prototype strain, GenBank accession number AY421764] and previously determined reference groups (RF-B, -C, -D, and -E). The optimal substitution models were Kimura two-parameter (K2P) with invariant sites (I) for 5′UTR and K2P with I- for VP4/2. Each sequence is identified by the country of origin, sample code, 3Dpol clade assignment and year of collection. Dot colors indicate the recombination group assignments based on 3Dpol phylogeny. Bars denote the evolutionary distance according to the number of nucleotide substitutions per site. Bootstrap consensus was inferred from 1,000 replicates.

Supplementary Figure S3. Association between VP1 sequence divergence and the proportion of recombinant comparisons.

Supplementary Figure S4. Divergence scan of nucleotide sequences between RF-A with other recombination groups (RF-F, -G, -H, -J, and -K). Thirty-nine complete genome sequences by RF groups obtained from this study were used, except RF-J and -K which were Chinese strains.

Table S1: Sequences information

Isolate	Country	City	Year	RF group	Accession number		
					Complete genome	VP1	3D
US/Gdula/I/1949	US	NS	1949	I	AY421764	-	-
FI/Se8926/A/2008	Finland	NS	2008	A	KP144346	-	-
FI/Se8925/A/2008	Finland	NS	2008	A	-	KP129346	KP129366
FI/Se8717/A/2008	Finland	NS	2008	A	KP144344	-	-
FI/Ta81126/A/2008	Finland	NS	2008	A	-	KP129337	KP129357
FI/Se8841/A/2008	Finland	NS	2008	A	KP144345	-	-
FI/Se8931/A/2008	Finland	NS	2008	A	-	KP129344	KP129364
FI/Tu81038/A/2008	Finland	NS	2008	A	-	KP129341	KP129361
FI/Ta81252/A/2008	Finland	NS	2008	A	-	KP129336	KP129356
FI/Ta8966/A/2008	Finland	NS	2008	A	-	KP129339	KP129359
FI/Tu81274/A/2008	Finland	NS	2008	A	-	KP129340	KP129360
FI/81163/A/2008	Finland	NS	2008	A	-	KP129335	KP129355
FI/Se8928/A/2008	Finland	NS	2008	A	-	KP129345	KP129365
FI/Tu81027/A/2008	Finland	NS	2008	A	-	KP129343	KP129363
FI/Finland/A/2008	Finland	NS	2008	A	KM114057	-	-
JP/Shizuoka18/A/2011	Japan	Shizuoka	2011	A	AB678778	-	-
UK/GlaV1/A/2014	UK	Glasgow	2014	A	KP144343	-	-
JP/Kyoto2/A/2003	Japan	Kyoto	2003	A	AB779616	-	-
JP/Kyoto3/A/2009	Japan	Kyoto	2009	A	AB779615	-	-
JP/Kyoto5/A/2009	Japan	Kyoto	2009	A	AB779618	-	-
UK/EdV1/A/2012	UK	Edinburgh	2012	A	KP144350	-	-
UK/EdV2/A/2012	UK	Edinburgh	2012	A	-	KP129347	KP129367
UK/EdV1/A/2010	UK	Edinburgh	2010	A	-	KP129348	KP129368
TW/409/A/2010	Taiwan	NS	2010	A	JQ946055	-	-
TW/1537/A/2011	Taiwan	NS	2011	A	JN582001	-	-
TW/391/A/2010	Taiwan	NS	2010	A	JQ946053	-	-
TW/399/A/2010	Taiwan	NS	2010	A	JQ946054	-	-
UK/EdV7/A/2013	UK	Edinburgh	2013	A	KP144342	-	-
UK/EdV13/A/2013	UK	Edinburgh	2013	A	KP144339	-	-
TH/CU25/A/2008	Thailand	Bangkok	2008	A	KX212500	KX212346	KX212536
TH/CU47/A/2009	Thailand	Bangkok	2009	A	KX212498	KX212344	KX212534
TH/CU83/A/2010	Thailand	Bangkok	2010	A	KX212495	KX212341	KX212531
TH/CU84/A/2010	Thailand	Bangkok	2010	A	KX212496	KX212342	KX212532
TH/CU86/A/2010	Thailand	Bangkok	2010	A	KX212499	KX212345	KX212535
TH/CU1499/A/2014	Thailand	Bangkok	2014	A	KX212503	KX212338	KX212528
TH/CU1508/A/2014	Thailand	Bangkok	2014	A	KX212504	KX212403	KX212593
TH/CU1420/A/2014	Thailand	Bangkok	2014	A	-	KX212380	KX212570
TH/CU1555/A/2014	Thailand	Khon kaen	2014	A	-	KX212404	KX212594
TH/CU1430/A/2014	Thailand	Bangkok	2014	A	-	KX212384	KX212574
TH/CU1271/A/2014	Thailand	Bangkok	2014	A	KX212505	KX212405	KX212595
TH/CU1443/A/2014	Thailand	Bangkok	2014	A	-	KX212385	KX212575
TH/CU1364/A/2014	Thailand	Bangkok	2014	A	-	KX212379	KX212569
TH/CU1379/A/2014	Thailand	Khon kaen	2014	A	-	KX212409	KX212599

TH/CU1483/A/2014	Thailand	Khon kaen	2014	A	-	KX212410	KX212600
TH/CU1552/A/2014	Thailand	Khon kaen	2014	A	-	KX212408	KX212598
TH/CU1433/A/2014	Thailand	Bangkok	2014	A	-	KX212417	KX212607
TH/CU1474/A/2014	Thailand	Bangkok	2014	A	-	KX212387	KX212577
TH/CU1393/A/2014	Thailand	Bangkok	2014	A	-	KX212378	KX212568
TH/CU1327/A/2014	Thailand	Bangkok	2014	A	-	KX212391	KX212581
TH/CU1421/A/2014	Thailand	Bangkok	2014	A	-	KX212396	KX212586
TH/CU1695/A/2015	Thailand	Bangkok	2015	A	-	KX212422	KX212612
TH/CU1278/A/2014	Thailand	Bangkok	2014	A	-	KX212419	KX212609
TH/CU1428/A/2014	Thailand	Bangkok	2014	A	-	KX212399	KX212589
TH/CU1389/A/2014	Thailand	Bangkok	2014	A	-	KX212381	KX212571
TH/CU1288/A/2014	Thailand	Bangkok	2014	A	-	KX212373	KX212563
TH/CU1330/A/2014	Thailand	Bangkok	2014	A	-	KX212375	KX212565
TH/CU1365/A/2014	Thailand	Bangkok	2014	A	-	KX212374	KX212564
TH/CU1398/A/2014	Thailand	Bangkok	2014	A	-	KX212418	KX212608
TH/CU1324/A/2014	Thailand	Bangkok	2014	A	-	KX212386	KX212576
TH/CU1373/A/2014	Thailand	Khon kaen	2014	A	-	KX212407	KX212597
TH/CU1292/A/2014	Thailand	Bangkok	2014	A	-	KX212402	KX212592
TH/CU1257/A/2014	Thailand	Bangkok	2014	A	-	KX212383	KX212573
DK/M22061/A/2014	Denmark	NS	2014	A	-	KX212411	KX212601
DK/F49465/A/2014	Denmark	NS	2014	A	-	KX212412	KX212602
DK/W38361/A/2014	Denmark	NS	2014	A	-	KX212413	KX212603
TH/CU1353/A/2014	Thailand	Khon kaen	2014	A	-	KX212420	KX212610
TH/CU1362/A/2014	Thailand	Bangkok	2014	A	-	KX212395	KX212585
TH/CU1391/A/2014	Thailand	Bangkok	2014	A	-	KX212406	KX212596
TH/CU1504/A/2014	Thailand	Bangkok	2014	A	-	KX212421	KX212611
DK/H36898/A/2014	Denmark	NS	2014	A	-	KX212416	KX212606
DK/T53016/A/2014	Denmark	NS	2014	A	-	KX212414	KX212604
TH/CU1608/A/2014	Thailand	Bangkok	2014	A	-	KX212393	KX212583
TH/CU1624/A/2015	Thailand	Bangkok	2015	A	-	KX212394	KX212584
TH/CU1548/A/2014	Thailand	Bangkok	2014	A	-	KX212392	KX212582
TH/CU1590/A/2014	Thailand	Bangkok	2014	A	-	KX212397	KX212587
TH/CU1599/A/2014	Thailand	Bangkok	2014	A	-	KX212398	KX212588
TH/CU1665/A/2015	Thailand	Bangkok	2015	A	-	KX212388	KX212578
TH/CU1302/A/2014	Thailand	Bangkok	2014	A	KX212501	KX212389	KX212579
TH/CU1648/A/2015	Thailand	Bangkok	2015	A	KX212502	KX212415	KX212605
TH/CU1558/A/2014	Thailand	Khon kaen	2014	A	-	KX212390	KX212580
TH/CU1296/A/2014	Thailand	Bangkok	2014	A	KX212506	KX212400	KX212590
TH/CU1493/A/2014	Thailand	Bangkok	2014	A	-	KX212401	KX212591
TH/CU1360/A/2014	Thailand	Bangkok	2014	A	-	KX212376	KX212566
TH/CU1404/A/2014	Thailand	Bangkok	2014	A	-	KX212377	KX212567
DK/T27464/A/2014	Denmark	NS	2014	A	-	KX212426	KX212616
ES/41833/A/2013	Spain	Teruel	2013	A	-	KX212425	KX212615
ES/40068/A/2013	Spain	Mallorca	2013	A	-	KX212427	KX212617
ES/41830/A/2013	Spain	Teruel	2013	A	-	KX212424	KX212614
ES/41816/A/2013	Spain	Teruel	2013	A	-	KX212423	KX212613
ES/41814/A/2013	Spain	Teruel	2013	A	-	KX212429	KX212619

DE/G4/A/2014	Germany	NS	2014	A	KX212508	KX212428	KX212618
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ES/07754/A/2013	Spain	Salamanca	2013	A	-	KX212430	KX212620
ES/07766/A/2013	Spain	Salamanca	2013	A	-	KX212433	KX212623
ES/07767/A/2013	Spain	Salamanca	2013	A	-	KX212431	KX212621
ES/07726/A/2013	Spain	Salamanca	2013	A	-	KX212432	KX212622
DK/W17257/A/2014	Denmark	NS	2014	A	-	KX212434	KX212624
DE/G3/A/2014	Germany	NS	2014	A	KX212509	KX212435	KX212625
TH/CU1268/A/2014	Thailand	Bangkok	2014	A	-	KX212436	KX212626
TH/CU1307/A/2014	Thailand	Bangkok	2014	A	-	KX212437	KX212627
ES/14623/A/2013	Spain	Mallorca	2013	A	-	KX212351	KX212541
DE/G1/A/2014	Germany	NS	2014	A	-	KX212350	KX212540
DK/M2489/A/2014	Denmark	NS	2014	A	-	KX212354	KX212544
TH/CU1249/A/2014	Thailand	Bangkok	2014	A	-	KX212365	KX212555
DK/M59573/A/2014	Denmark	NS	2014	A	-	KX212352	KX212542
DK/W22166/A/2014	Denmark	NS	2014	A	-	KX212371	KX212561
TH/CU1251/A/2014	Thailand	Bangkok	2014	A	-	KX212357	KX212547
TH/CU1559/A/2014	Thailand	Bangkok	2014	A	-	KX212366	KX212556
DK/W21152/A/2014	Denmark	NS	2014	A	-	KX212353	KX212543
TH/CU1368/A/2014	Thailand	Bangkok	2014	A	KX212494	KX212368	KX212558
TH/CU1464/A/2014	Thailand	Bangkok	2014	A	-	KX212358	KX212548
TH/CU1270/A/2014	Thailand	Bangkok	2014	A	-	KX212369	KX212559
TH/CU1326/A/2014	Thailand	Bangkok	2014	A	-	KX212361	KX212551
TH/CU1382/A/2014	Thailand	Bangkok	2014	A	-	KX212359	KX212549
TH/CU1406/A/2014	Thailand	Bangkok	2014	A	KX212493	KX212364	KX212554
TH/CU1352/A/2014	Thailand	Bangkok	2014	A	-	KX212360	KX212550
TH/CU1427/A/2014	Thailand	Khon kaen	2014	A	-	KX212356	KX212546
TH/CU1519/A/2014	Thailand	Bangkok	2014	A	KX212492	KX212370	KX212560
TH/CU1318/A/2014	Thailand	Bangkok	2014	A	-	KX212367	KX212557
TH/CU1328/A/2014	Thailand	Bangkok	2014	A	-	KX212362	KX212552
TH/CU1298/A/2014	Thailand	Bangkok	2014	A	-	KX212363	KX212553
TH/CU1243/A/2014	Thailand	Bangkok	2014	A	KX212491	KX212355	KX212545
TH/CU1596/A/2014	Thailand	Bangkok	2014	A	-	KX212372	KX212562
DK/W15075/A/2014	Denmark	NS	2014	A	-	KX212348	KX212538
DK/S45898/A/2014	Denmark	NS	2014	A	-	KX212349	KX212539
TH/CU160/A/2012	Thailand	Bangkok	2012	A	KX212497	KX212343	KX212533
TH/CU209/A/2012	Thailand	Bangkok	2012	A	KX212489	KX212339	KX212529
TH/CU262/A/2012	Thailand	Bangkok	2012	A	KX212490	KX212340	KX212530
SE/116246/A/2014	Sweden	Stockholm	2014	A	-	KX212488	KX212673
SE/116413/A/2014	Sweden	Stockholm	2014	A	-	KX212483	KX212674
SE/117236/A/2014	Sweden	Stockholm	2014	A	-	KX212484	KX212675
SE/117446/A/2014	Sweden	Stockholm	2014	A	-	KX212485	KX212676
SE/506607/A/2014	Sweden	Stockholm	2014	A	-	KX212486	KX212677
SE/510615/A/2014	Sweden	Stockholm	2014	A	-	KX212487	KX212678
CN/P115/A/2013	China	Wenzhou	2013	A	KP289367	-	-
CN/P169/A/2013	China	Wenzhou	2013	A	KP289369	-	-
CN/P2/A/2013	China	Wenzhou	2013	A	KP289370	-	-

CN/P223/A/2013	China	Wenzhou	2013	A	KP289371	-	-
CN/P225/A/2013	China	Wenzhou	2013	A	KP289372	-	-
CN/P246/A/2013	China	Wenzhou	2013	A	KP289373	-	-
CN/P345/A/2013	China	Wenzhou	2013	A	KP289376	-	-
CN/P358/A/2013	China	Wenzhou	2013	A	KP289377	-	-
CN/P360/A/2013	China	Wenzhou	2013	A	KP289378	-	-
CN/P362/A/2013	China	Wenzhou	2013	A	KP289380	-	-
CN/P366/A/2013	China	Wenzhou	2013	A	KP289381	-	-
CN/P6/A/2013	China	Wenzhou	2013	A	KP289384	-	-
CN/P66/A/2013	China	Wenzhou	2013	A	KP289385	-	-
CN/P702/A/2013	China	Wenzhou	2013	A	KP289388	-	-
CN/P731/A/2013	China	Wenzhou	2013	A	KP289390	-	-
CN/SZc173/A/2013	China	Shenzhen	2013	A	KF682362	-	-
CN/SZc294/A/2013	China	Shenzhen	2013	A	KF682363	-	-
CN/5084SH/A/2013	China	Shanghai	2013	A	KJ541154	-	-
CN/PF19SH/A/2013	China	Shanghai	2013	A	KJ541155	-	-
CN/5047SH/A/2013	China	Shanghai	2013	A	KJ541156	-	-
CN/4645SH/A/2013	China	Shanghai	2013	A	KJ541157	-	-
CN/5069SH/A/2013	China	Shanghai	2013	A	KJ541158	-	-
CN/4592SH/A/2013	China	Shanghai	2013	A	KJ541159	-	-
CN/PF001SH/A/2013	China	Shanghai	2013	A	KJ541165	-	-
CN/1827SH/A/2013	China	Shanghai	2013	A	KJ541166	-	-
CN/1232SH/A/2013	China	Shanghai	2013	A	KJ541167	-	-
CN/3913SH/A/2013	China	Shanghai	2013	A	KJ541168	-	-
CN/4368SH/A/2013	China	Shanghai	2013	A	KJ541169	-	-
CN/12743GZ/A/2013	China	Guangzhou	2013	A	KR815992	-	-
FI/TS3FinTu81042/B/2008	Finland	NS	2008	B	-	KP129342	KP129362
JP/Kyoto1/B/1999	Japan	Kyoto	1999	B	AB779614	-	-
JP/Kyoto4/C/2009	Japan	Kyoto	2009	C	AB779617	-	-
CN/HN421/D/2011	China	Henan	2011	D	JQ964234	-	-
TW/295/E/2009	Taiwan	NS	2009	E	JQ946052	-	-
TW/273/E/2009	Taiwan	NS	2009	E	JQ946051	-	-
TW/20/E/2009	Taiwan	NS	2009	E	JQ946050	-	-
TW/00141/E/2007	Taiwan	NS	2007	E	KR706309	-	-
UK/EdV13/F/2012	UK	Edinburgh	2012	F	KP144341	-	-
UK/EdV12/F/2013	UK	Edinburgh	2013	F	KP144340	-	-
DK/S48908/F/2014	Denmark	NS	2014	F	KX212510	KX212438	KX212628
DK/T52656/F/2014	Denmark	NS	2014	F	-	KX212439	KX212629
TH/CU1256/F/2014	Thailand	Bangkok	2014	F	KX212519	KX212460	KX212650
DK/S43334/F/2014	Denmark	NS	2014	F	KX212511	KX212441	KX212631
DE/G2/F/2014	Germany	NS	2014	F	KX212512	KX212442	KX212632
ES/06707/F/2014	Spain	Mallorca	2014	F	KX212513	KX212440	KX212630
TH/CU1383/F/2014	Thailand	Bangkok	2014	F	-	KX212463	KX212653
TH/CU1422/F/2014	Thailand	Bangkok	2014	F	-	KX212464	KX212654
TH/CU1440/F/2014	Thailand	Bangkok	2014	F	-	KX212467	KX212657
TH/CU1260/F/2014	Thailand	Bangkok	2014	F	KX212518	KX212462	KX212652
TH/CU1385/F/2014	Thailand	Bangkok	2014	F	-	KX212461	KX212651

TH/CU1407/F/2014	Thailand	Bangkok	2014	F	-	KX212470	KX212660
TH/CU1435/F/2014	Thailand	Bangkok	2014	F	-	KX212471	KX212661
TH/CU1265/F/2014	Thailand	Bangkok	2014	F	-	KX212469	KX212659
TH/CU1310/F/2014	Thailand	Bangkok	2014	F	-	KX212468	KX212658
TH/CU1526/F/2014	Thailand	Bangkok	2014	F	KX212517	KX212473	KX212663
TH/CU1392/F/2014	Thailand	Bangkok	2014	F	-	KX212447	KX212637
TH/CU1466/F/2014	Thailand	Bangkok	2014	F	-	KX212446	KX212636
TH/CU1329/F/2014	Thailand	Bangkok	2014	F	-	KX212458	KX212648
TH/CU1331/F/2014	Thailand	Bangkok	2014	F	KX212515	KX212448	KX212638
TH/CU1498/F/2014	Thailand	Bangkok	2014	F	-	KX212452	KX212642
TH/CU1332/F/2014	Thailand	Bangkok	2014	F	-	KX212451	KX212641
TH/CU1503/F/2014	Thailand	Bangkok	2014	F	-	KX212453	KX212643
TH/CU1465/F/2014	Thailand	Bangkok	2014	F	-	KX212445	KX212635
TH/CU1423/F/2014	Thailand	Khon kaen	2014	F	KX212516	KX212459	KX212649
TH/CU1426/F/2014	Thailand	Khon kaen	2014	F	-	KX212450	KX212640
TH/CU1424/F/2014	Thailand	Khon kaen	2014	F	-	KX212449	KX212639
TH/CU1350/F/2014	Thailand	Bangkok	2014	F	-	KX212455	KX212645
TH/CU1376/F/2014	Thailand	Bangkok	2014	F	-	KX212457	KX212647
TH/CU1372/F/2014	Thailand	Bangkok	2014	F	-	KX212465	KX212655
TH/CU1375/F/2014	Thailand	Bangkok	2014	F	-	KX212456	KX212646
TH/CU1374/F/2014	Thailand	Bangkok	2014	F	-	KX212466	KX212656
TH/CU1556/F/2014	Thailand	Khon kaen	2014	F	-	KX212472	KX212662
TH/CU796/F/2012	Thailand	Bangkok	2012	F	KX212514	KX212347	KX212537
UK/EdV2/G/2011	UK	Edinburgh	2011	G	KP144351	-	-
UK/EdV3/G/2013	UK	Edinburgh	2013	G	KP144353	-	-
UK/EdV11/G/2013	UK	Edinburgh	2013	G	KP144352	-	-
UK/EdV1/G/2011	UK	Edinburgh	2011	G	KP144349	-	-
DK/M22416/G/2014	Denmark	NS	2014	G	KX212526	KX212475	KX212665
ES/00507/G/2014	Spain	Mallorca	2014	G	-	KX212474	KX212664
DK/T24787/G/2014	Denmark	NS	2014	G	KX212527	KX212476	KX212666
UK/EdV12/H/2014	UK	Edinburgh	2014	H	-	KP129352	KP129374
UK/EdV1/H/2014	UK	Edinburgh	2014	H	-	KP129354	KP129373
UK/EdV2/H/2014	UK	Edinburgh	2014	H	-	KP129353	KP129372
UK/EdV16/H/2014	UK	Edinburgh	2014	H	KP144347	-	-
UK/EdV4/H/2014	UK	Edinburgh	2014	H	KP144348	-	-
UK/EdV6/H/2014	UK	Edinburgh	2014	H	KP129370	-	-
DK/S52397/H/2014	Denmark	NS	2014	H	KX212524	KX212477	KX212667
DK/T22324/H/2014	Denmark	NS	2014	H	KX212525	KX212480	KX212670
DK/H15054/H/2014	Denmark	NS	2014	H	KX212522	KX212479	KX212669
DK/T36724/H/2014	Denmark	NS	2014	H	KX212523	KX212478	KX212668
ES/06417/H/2014	Spain	Vigo	2014	H	KX212521	KX212482	KX212672
ES/04587/H/2013	Spain	Madrid	2013	H	KX212520	KX212481	KX212671
CN/P143/J/2013	China	Wenzhou	2013	J	KP289368	-	-
CN/P278/J/2013	China	Wenzhou	2013	J	KP289374	-	-
CN/P309/J/2013	China	Wenzhou	2013	J	KP289375	-	-
CN/P361/J/2013	China	Wenzhou	2013	J	KP289379	-	-
CN/P406/J/2013	China	Wenzhou	2013	J	KP289382	-	-

CN/P426/J/2013	China	Wenzhou	2013	J	KP289383	-	-
CN/P674/J/2013	China	Wenzhou	2013	J	KP289386	-	-
CN/P695/J/2013	China	Wenzhou	2013	J	KP289387	-	-
CN/P728/J/2013	China	Wenzhou	2013	J	KP289389	-	-
CN/P786/J/2013	China	Wenzhou	2013	J	KP289391	-	-
CN/P794/J/2013	China	Wenzhou	2013	J	KP289392	-	-
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CN/5056SH/J/2013	China	Shanghai	2013	J	KJ541161	-	-
CN/PF3SH/J/2013	China	Shanghai	2013	J	KJ541162	-	-
CN/PF1SH/J/2013	China	Shanghai	2013	J	KJ612513	-	-
CN/P289/K/2013	China	Wenzhou	2013	K	KP289365	-	-
CN/P423/K/2013	China	Wenzhou	2013	K	KP289366	-	-
CN/P874/K/2013	China	Wenzhou	2013	K	KP289393	-	-
CN/CC13/K/2013	China	Changchun	2013	K	KM279379	-	-

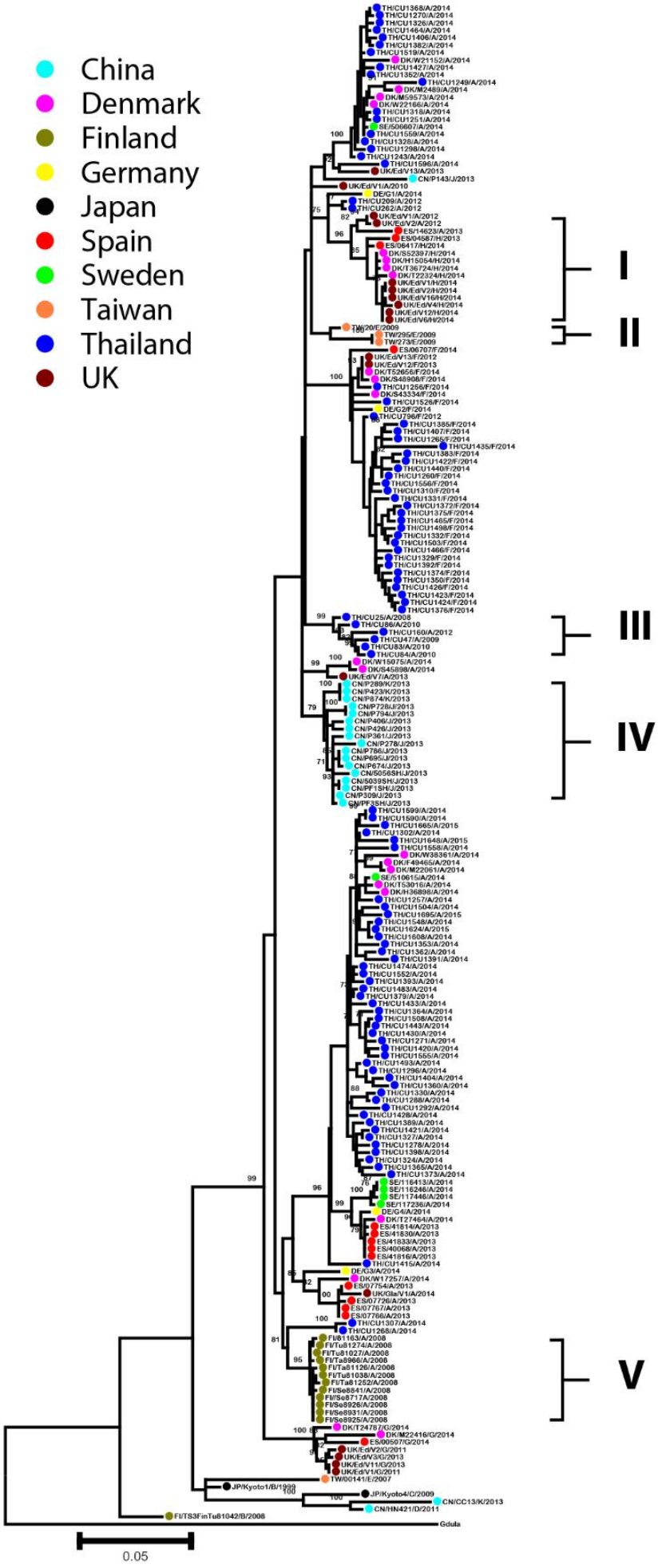
NS: non specified

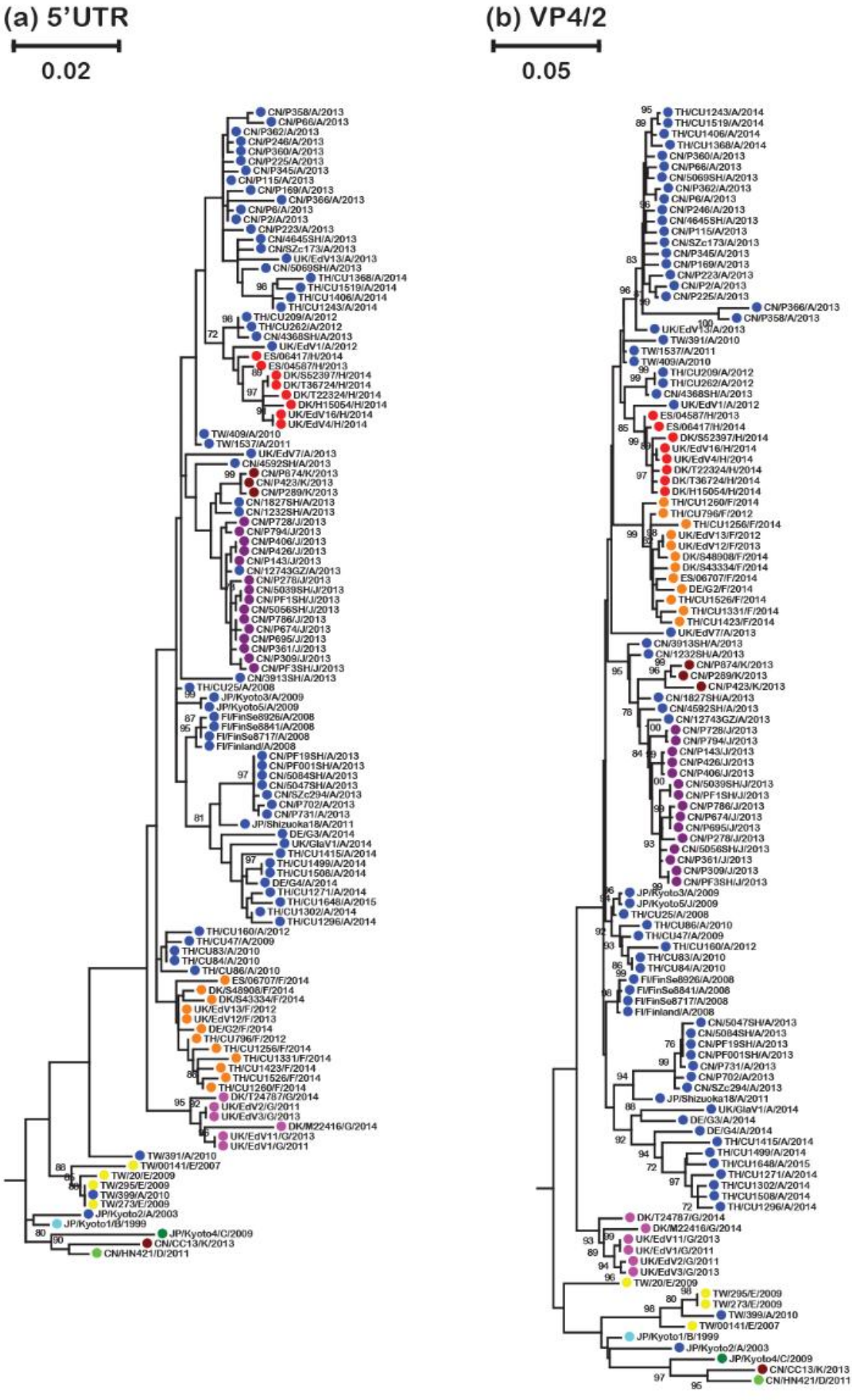
Table S2: Primer set used for whole genome amplification by nested RT-PCR

No.	Primer	Sequence (5' to 3')	Position
1	CAV6-F39/OS	ACT GGG CGC YAG CAC ACT GAT TC	39 - 61
	CAV6-R1673/OAS	AGT TAR TGT RAT TGG YAC YTC TGT	1650 - 1673
	CAV6-F55/IS	CTG ATT CTA YGG AAY CTT TGT GCG	55 - 78
	CAV6-R1567/IAS	GGA AGY GCR TTR ACA TAT GGC AT	1545 - 1567
2	CAV6-F1266/OS	TCG GGY TTC TGY ATG CAY GTT CA	1266 - 1288
	CAV6-R2806/OAS	GAY AGT TCT AGY TTG CGC CGC TG	2784 - 2806
	CAV6-F1290/IS	TGY AAY GCR AGC AAR TTC CAT CA	1290 - 1312
	CAV6-R2727/IAS	CCG AGT CCT TYA CCT CCA CAA C	2706 - 2727
3	CAV6-F2458/OS	CRA ATG CDG TGG AAA GYG CTG T	2458 - 2479
	CAV6-R3832/OAS	CCT TTG ATR TAA TCW GAY ACD CC	3810 - 3832
	CAV6-F2485/IS	GCR CTY GCT GAY ACC ACA ATA TC	2485 - 2506
	CAV6-R3816/IAS	GAC ACC CTG YTC CAT RGC TTC	3795 - 3816
4	CAV6-F3498/OS	GCT CAR GGA TGT GAY ACY ATT GC	3498 - 3520
	CAV6-R4564/OAS	CTA GAG TGR TAY TTR TCR GCT AT	4542 - 4564
	CAV6-F3603/IS	GTC TTY GTG GAA GCT AGT GAG TA	3603 - 3625
	CAV6-R4463/IAS	ACG GTG TTT GCT CTT GAA CTG CAT	4440 - 4463
5	CAV6-F4107/OS	AGY GCA TCN TGG CTH AAG AAG TT	4107 - 4129
	CAV6-R5482/OAS	TGA TCY GTY TGV ACY TGC CTR AT	5460 - 5482
	CAV6-F4214/IS	TRT ACC AGC AGC TAA AGA GAA GGT	4214 - 4237
	CAV6-R5330/IAS	GTA GAT RAC ATA CAC CAR TGA RAC	5307 - 5330
6	CAV6-F4994/OS	ATC CAA RGT BAG RTA YAG TGT GGA	4994 - 5017
	CAV6-R6422/OAS	GAG RTC AAR DCC ATA CTT RTC CAT	6399 - 6422
	CAV6-F5061/IS	GCY ATT GGN AAC ACA ATC GAA GC	5061 - 5083
	CAV6-R6364/IAS	GGG TCY AAR ATG TCY CTC TTC TT	6342 - 6364

Table S3. Recombination groups (RF-A to -K) identified in different countries based on phylogenetic analysis of the 3Dpol region**.**

Country	RF-A	RF-B	RF-C	RF-D	RF-E	RF-F	RF-G	RF-H	RF-J	RF-K	Total
All	105					37	3	6			151
Denmark	13					3	2	4			22
Germany	3					1					4
Spain	10					1	1	2			14
Sweden	6										6
Thailand	73					32					105


China
Denmark
Finland
Germany
Japan
Spain
Sweden
Taiwan
Thailand
UK
I
II
III
IV
V
0.05


(a) 5'UTR
0.02
CN/P358/A/2013
CN/P66/A/2013
CN/P362/A/2013
CN/P246/A/2013
CN/P360/A/2013
CN/P225/A/2013
CN/P345/A/2013
CN/P115/A/2013
CN/P169/A/2013
CN/P366/A/2013
CN/P6/A/2013
CN/P2/A/2013
CN/P223/A/2013
CN/4645SH/A/2013
CN/SZc173/A/2013
UK/EdV13/A/2013
CN/5069SH/A/2013
TH/CU1368/A/2014
TH/CU1519/A/2014
TH/CU1406/A/2014
TH/CU1243/A/2014
TH/CU209/A/2012
TH/CU262/A/2012
CN/4368SH/A/2013
UK/EdV1/A/2012
ES/06417/H/2014
ES/04587/H/2013
DK/S52397/H/2014
DK/T36724/H/2014
DK/T22324/H/2014
DK/H15054/H/2014
UK/EdV16/H/2014
UK/EdV4/H/2014
TW/409/A/2010
TW/1537/A/2011
UK/EdV7/A/2013
CN/4592SH/A/2013
CN/P874/K/2013
CN/P423/K/2013
CN/P289/K/2013
CN/1827SH/A/2013
CN/1232SH/A/2013
CN/P728/J/2013
CN/P794/J/2013
CN/P406/J/2013
CN/P426/J/2013
CN/P143/J/2013
CN/12743GZ/A/2013
CN/P278/J/2013
CN/5039SH/J/2013
CN/PF1SH/J/2013
CN/5056SH/J/2013
CN/P786/J/2013
CN/P674/J/2013
CN/P695/J/2013
CN/P361/J/2013
CN/P309/J/2013
CN/PF3SH/J/2013
CN/3913SH/A/2013
TH/CU25/A/2008
JP/Kyoto3/A/2009
JP/Kyoto5/A/2009
FI/FinSe8926/A/2008
FI/FinSe8841/A/2008
FI/FinSe8717/A/2008
FI/Finland/A/2008
CN/PF19SH/A/2013
CN/PF001SH/A/2013
CN/5084SH/A/2013
CN/5047SH/A/2013
CN/SZc294/A/2013
CN/P702/A/2013
CN/P731/A/2013
JP/Shizuoka18/A/2011
DE/G3/A/2014
UK/GlaV1/A/2014
TH/CU1415/A/2014
TH/CU1499/A/2014
TH/CU1508/A/2014
DE/G4/A/2014
TH/CU1271/A/2014
TH/CU1648/A/2015
TH/CU1302/A/2014
TH/CU1296/A/2014
TH/CU160/A/2012
TH/CU47/A/2009
TH/CU83/A/2010
TH/CU84/A/2010
TH/CU86/A/2010
ES/06707/F/2014
DK/S48908/F/2014
DK/S43334/F/2014
UK/EdV13/F/2012
UK/EdV12/F/2013
DE/G2/F/2014
TH/CU796/F/2012
TH/CU1256/F/2014
TH/CU1331/F/2014
TH/CU1423/F/2014
TH/CU1526/F/2014
TH/CU1260/F/2014
DK/T24787/G/2014
UK/EdV2/G/2011
UK/EdV3/G/2013
DK/M22416/G/2014
UK/EdV11/G/2013
UK/EdV1/G/2011
TW/391/A/2010
TW/00141/E/2007
TW/20/E/2009
TW/295/E/2009
TW/399/A/2010
TW/273/E/2009
JP/Kyoto2/A/2003
JP/Kyoto1/B/1999
JP/Kyoto4/C/2009
CN/CC13/K/2013
CN/HN421/D/2011
(b) VP4/2
0.05
TH/CU1243/A/2014
TH/CU1519/A/2014
TH/CU1406/A/2014
TH/CU1368/A/2014
CN/P360/A/2013
CN/P66/A/2013
CN/5069SH/A/2013
CN/P362/A/2013
CN/P6/A/2013
CN/P246/A/2013
CN/4645SH/A/2013
CN/P115/A/2013
CN/SZc173/A/2013
CN/P345/A/2013
CN/P169/A/2013
CN/P223/A/2013
CN/P2/A/2013
CN/P225/A/2013
CN/P366/A/2013
CN/P358/A/2013
UK/EdV13/A/2013
TW/391/A/2010
TW/1537/A/2011
TW/409/A/2010
TH/CU209/A/2012
TH/CU262/A/2012
CN/4368SH/A/2013
UK/EdV1/A/2012
ES/04587/H/2013
ES/06417/H/2014
DK/S52397/H/2014
UK/EdV16/H/2014
UK/EdV4/H/2014
DK/T22324/H/2014
DK/T36724/H/2014
DK/H15054/H/2014
TH/CU1260/F/2014
TH/CU796/F/2012
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UK/EdV13/F/2012
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DE/G2/F/2014
TH/CU1526/F/2014
TH/CU1331/F/2014
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CN/3913SH/A/2013
CN/1232SH/A/2013
CN/P874/K/2013
CN/P289/K/2013
CN/P423/K/2013
CN/1827SH/A/2013
CN/4592SH/A/2013
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CN/P728/J/2013
CN/P794/J/2013
CN/P143/J/2013
CN/P426/J/2013
CN/P406/J/2013
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JP/Kyoto5/J/2009
TH/CU25/A/2008
TH/CU86/A/2010
TH/CU47/A/2009
TH/CU160/A/2012
TH/CU83/A/2010
TH/CU84/A/2010
FI/FinSe8926/A/2008
FI/FinSe8841/A/2008
FI/FinSe8717/A/2008
FI/Finland/A/2008
CN/5047SH/A/2013
CN/5084SH/A/2013
CN/PF19SH/A/2013
CN/PF001SH/A/2013
CN/P731/A/2013
CN/P702/A/2013
CN/SZc294/A/2013
JP/Shizuoka18/A/2011
UK/GlaV1/A/2014
DE/G3/A/2014
DE/G4/A/2014
TH/CU1415/A/2014
TH/CU1499/A/2014
TH/CU1648/A/2015
TH/CU1271/A/2014
TH/CU1302/A/2014
TH/CU1508/A/2014
TH/CU1296/A/2014
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TW/273/E/2009
TW/399/A/2010
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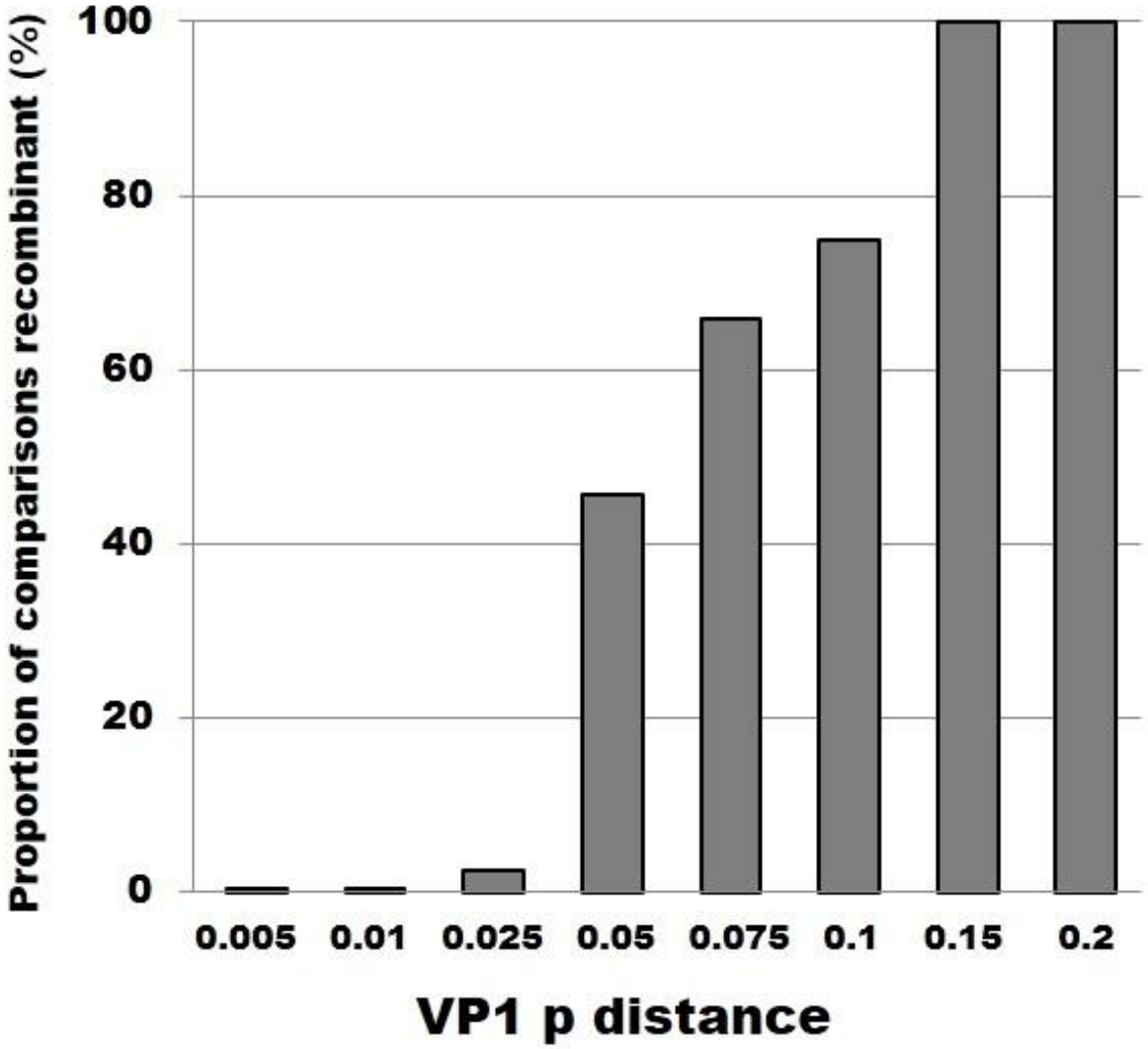
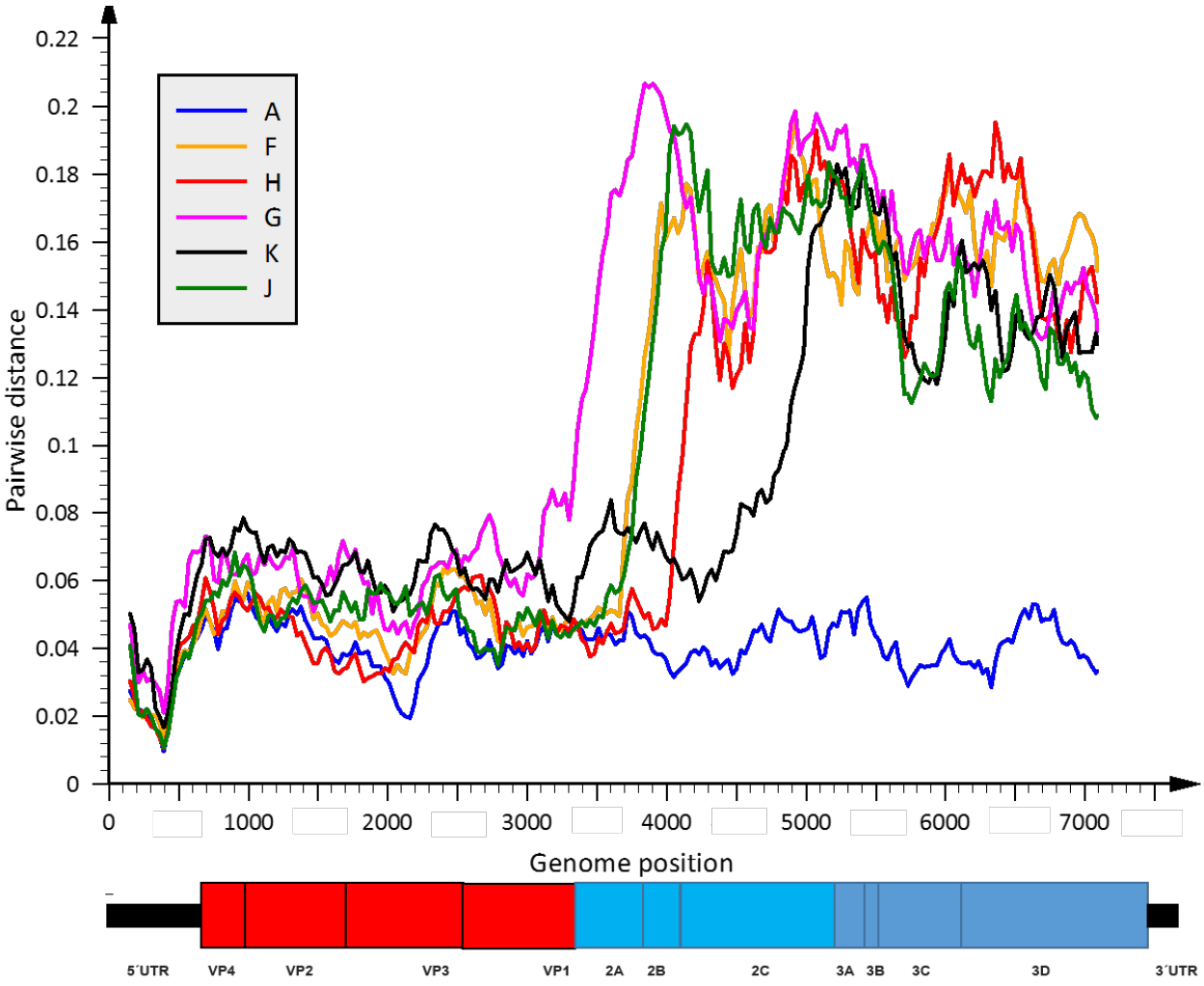
CN/CC13/K/2013
CN/HN421/D/2011


Proportion of comparisons recombinant (%)
100
80
60
40
20
0
0.005
0.01
0.025
0.05
0.075
0.1
0.15
0.2
VP1 p distance


Pairwise distance
0.22
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
A
F
H
G
K
J
0
1000
2000
3000
4000
5000
6000
7000
Genome position
5´UTR
VP4
VP2
VP3
VP1
2A
2B
2C
3A
3B
3C
3D
3´UTR