

SOM

FIG S1. Maximum likelihood (ML) trees of the PB2 (A), PB1 (B), PA (C), HA (D), NP (E), NA (F), M (G), and NS (H) segments. The reliability of all phylogenetic groupings of each tree was determined through a non-parametric bootstrap resampling analysis with Garli: 1000 replicates of ML trees were analyzed by applying GTR+ Γ 4+I model of nucleotide substitution. Bootstrap values with a support of $\geq 70\%$ are depicted on the ML trees. Scale bars roughly represent 5% of nucleotide substitutions between close relatives. The color-coding of viruses is based on the antigenic clusters of HA (1, 2). The images can be zoomed to show details.

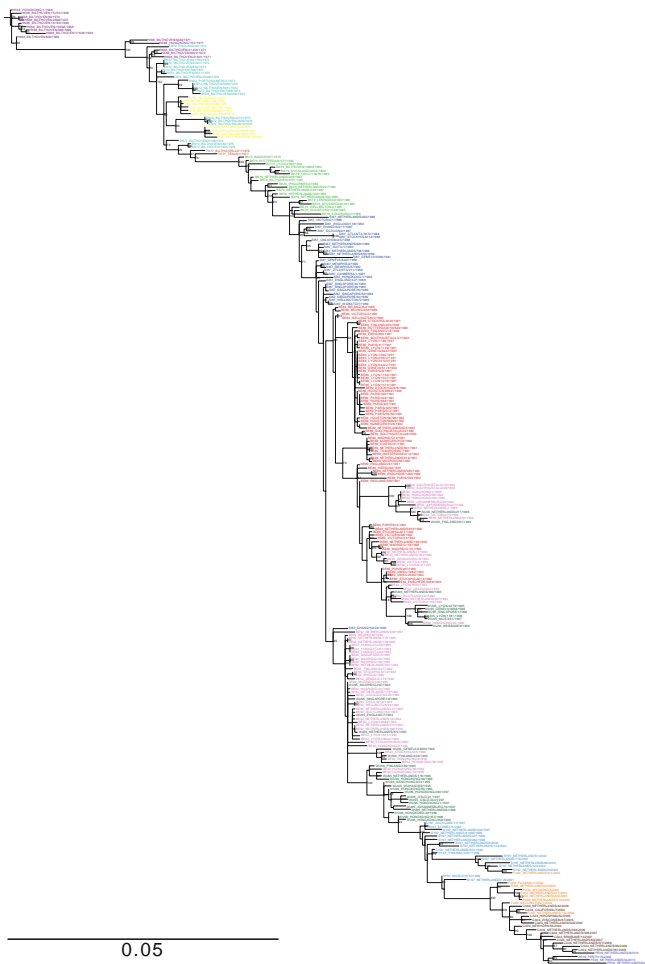


FIG S1A.

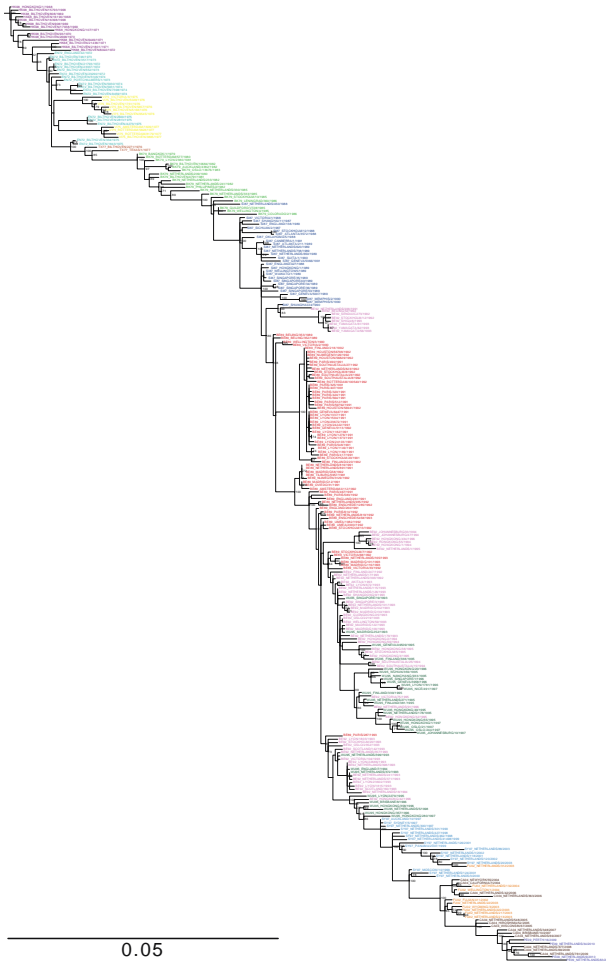


FIG S1B.

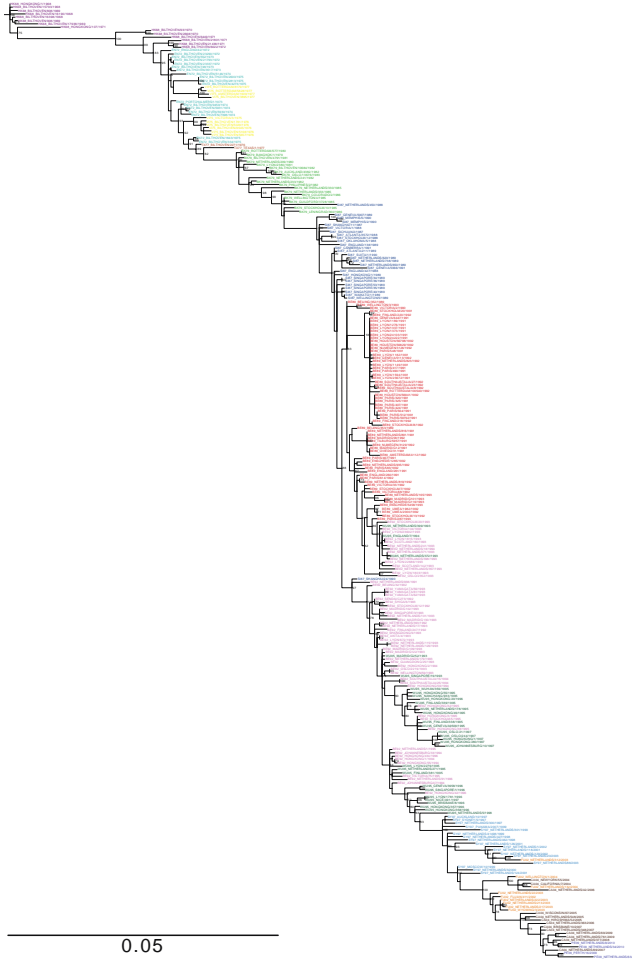


FIG S1C.

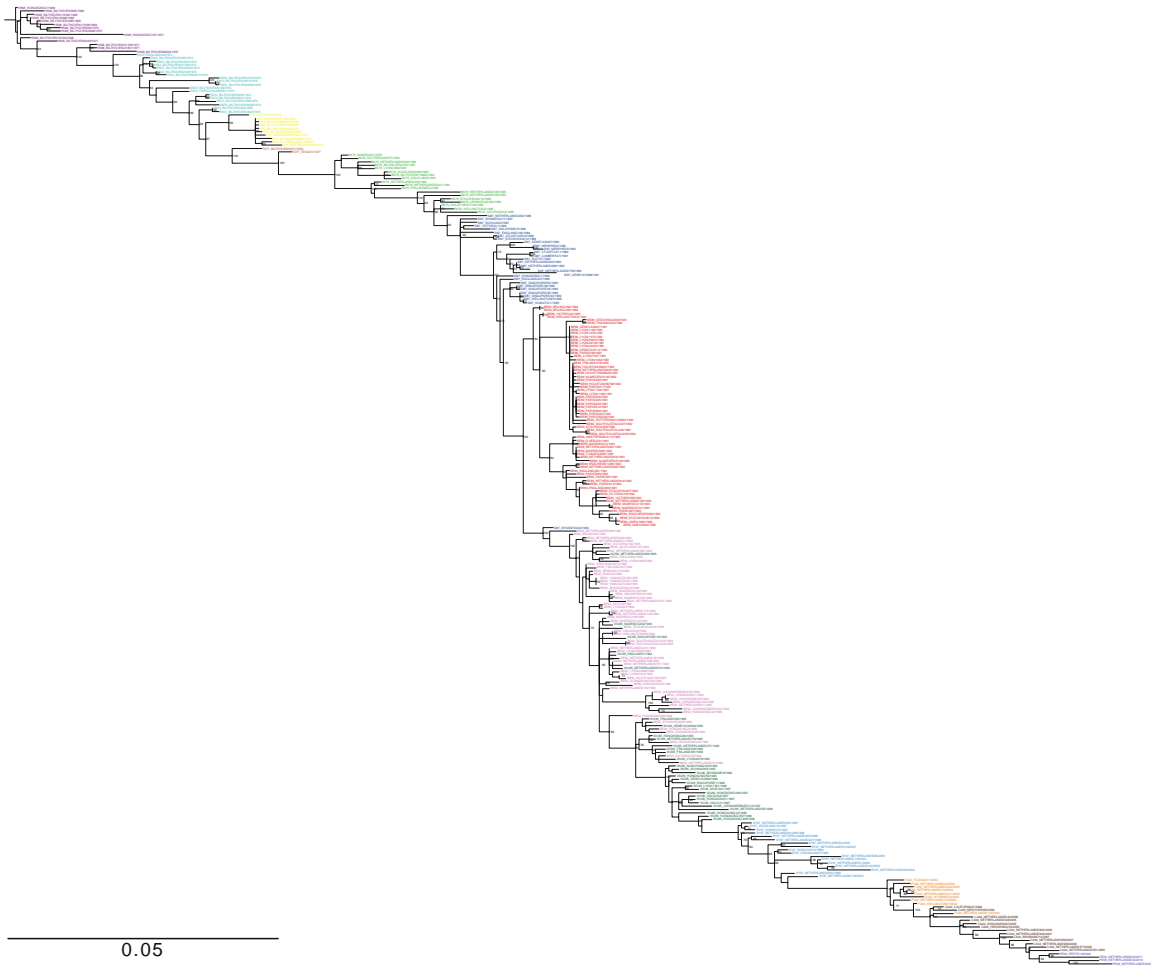


FIG S1D.

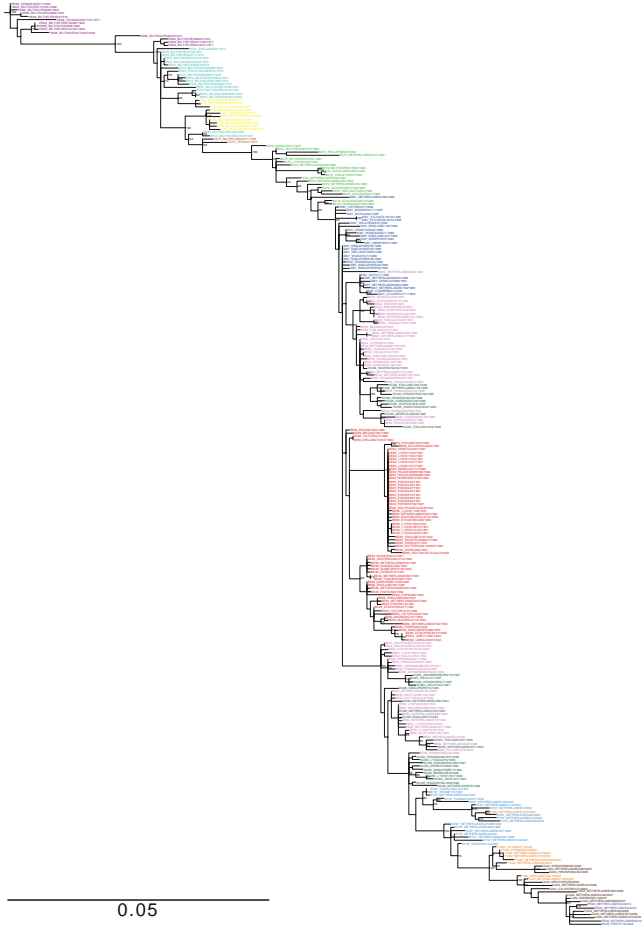


FIG S1E.

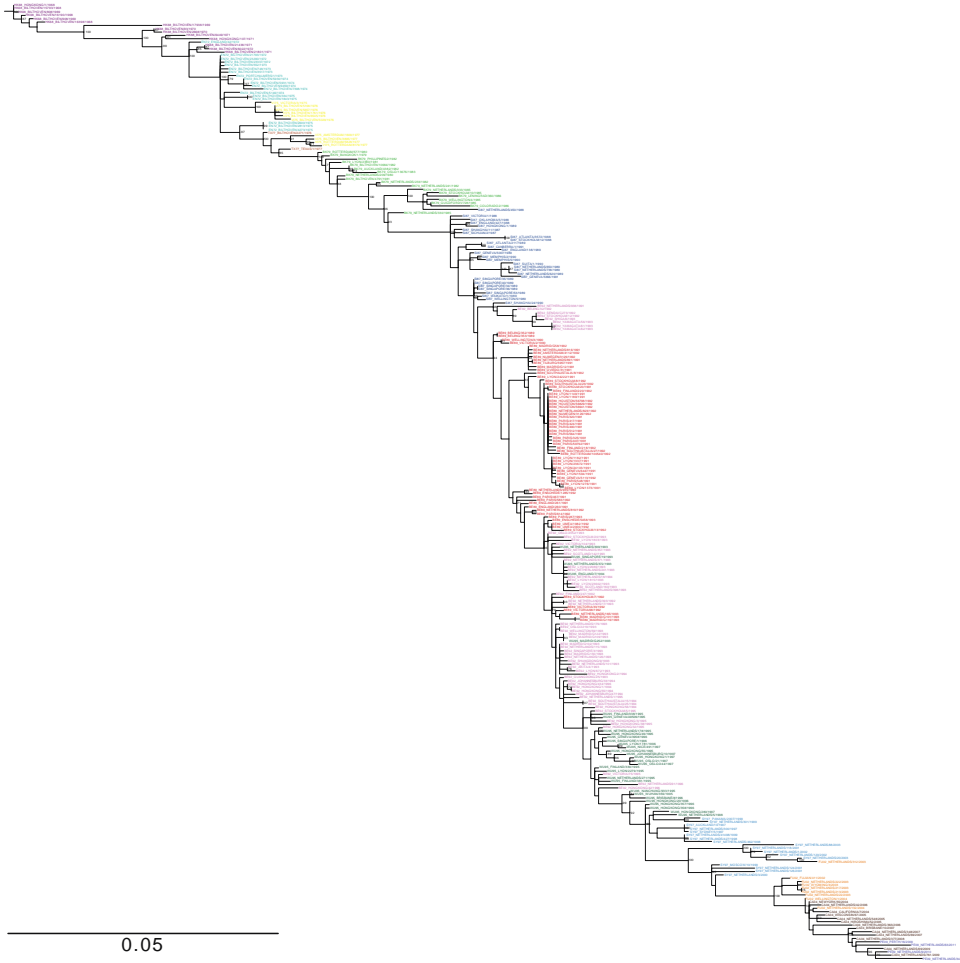


FIG S1F.



FIG S1G.



FIG S1H.

FIG S2. Alignments of PB2 (A), PB1 (B, left panel), PB1-F2 (B, right panel), PA (C, left panel), PA-X (C, right panel), HA (D), NP (E), NA (F), M1 (G, left panel), M2 (G, right panel), NS2 (H, left panel), and NEP (H, right panel) of A(H3N2) viruses used in this study. Alignments are grouped and color-coded according to the year of isolation and the antigenic clusters of HA (1, 2). PB1-N4 (B, left panel), PA-N155 (C, left panel), PA-N182 (C, left panel), HA1 (D), and HA2 (D) are indicated with a black border. Stop codons are shown as asterisks and within black borders. Codons in which there were no amino acid substitutions were excluded. The images can be zoomed to show details.

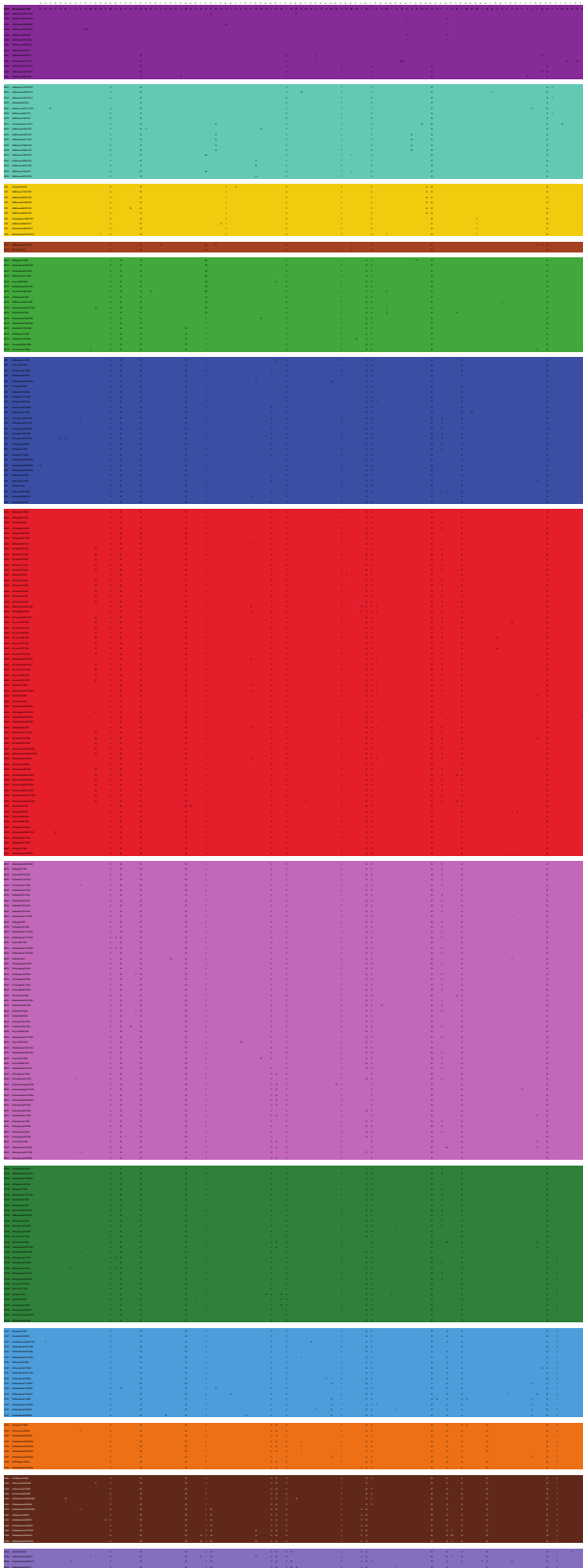


FIG S2A.

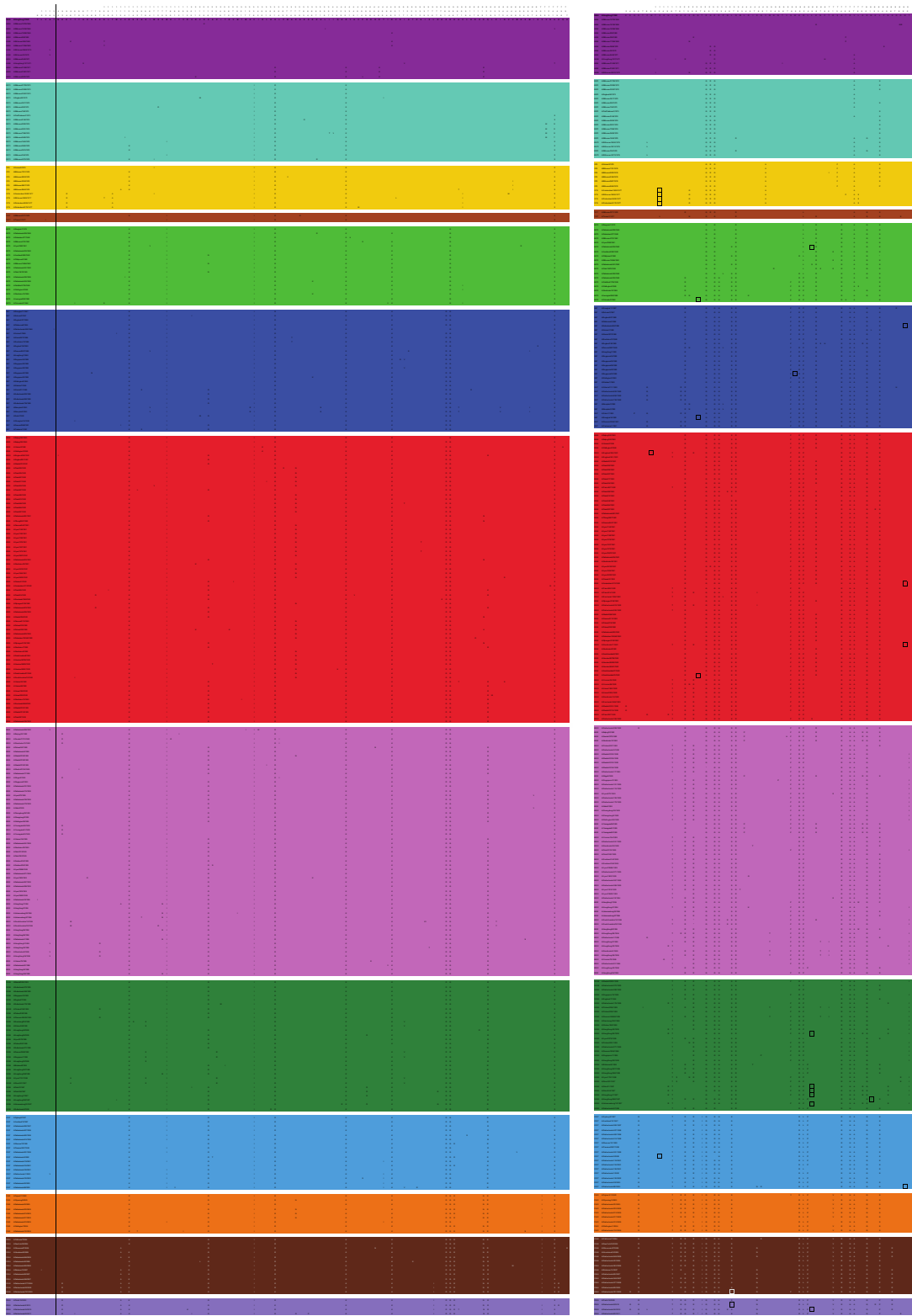


FIG S2B.



FIG S2C.

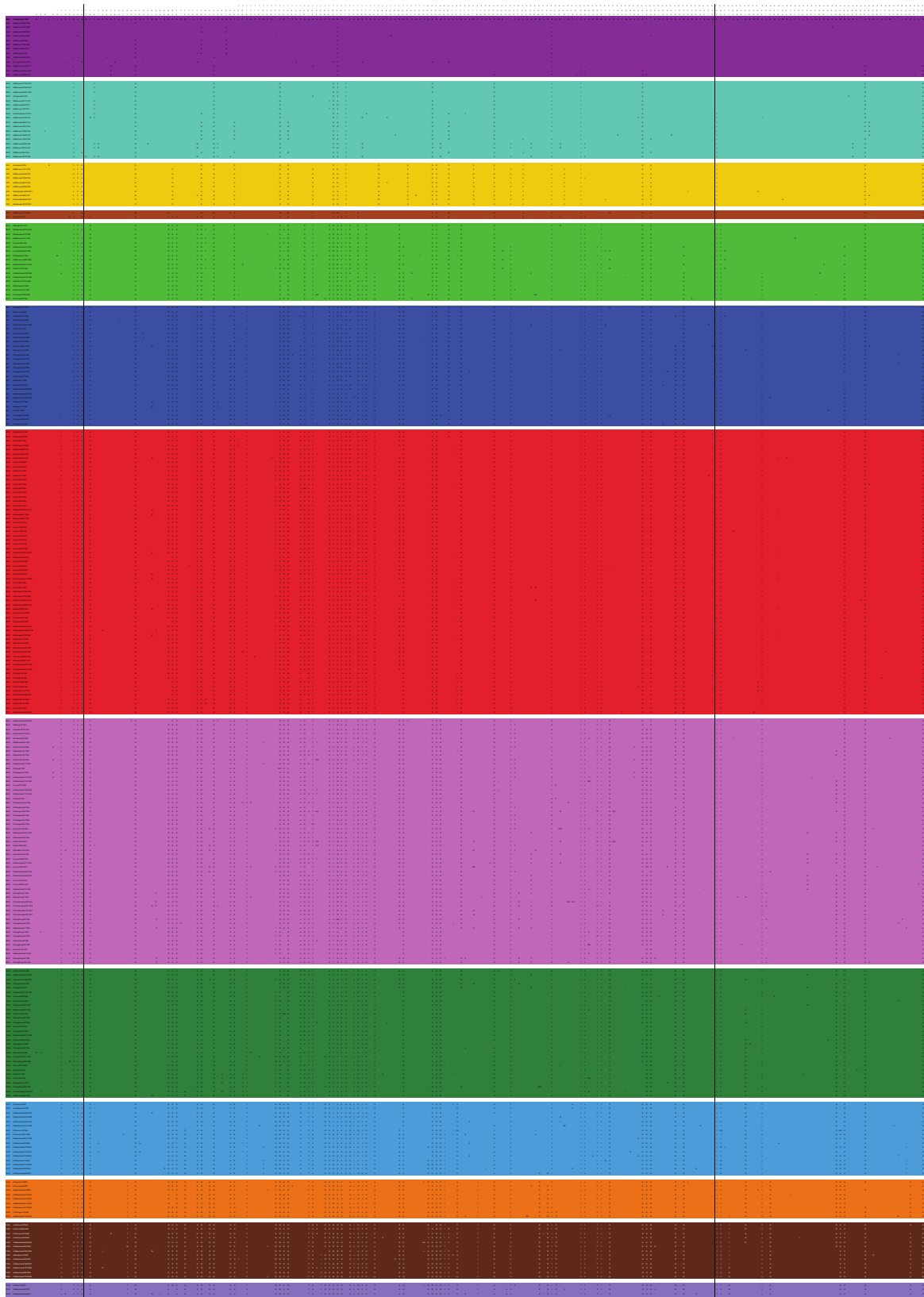


FIG S2D.

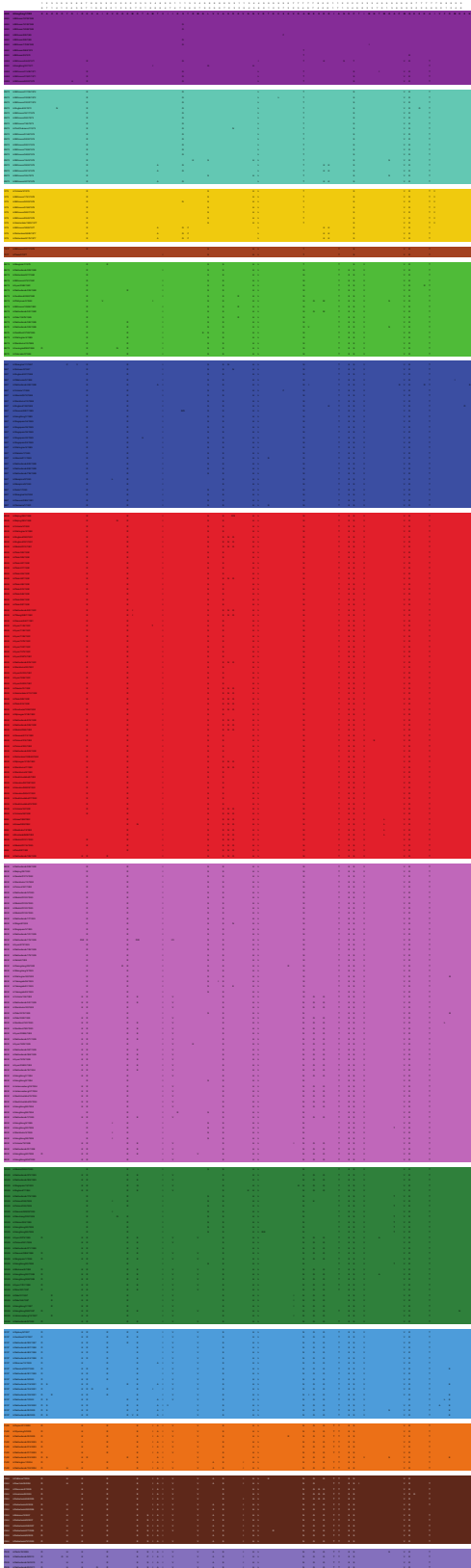


FIG S2E.

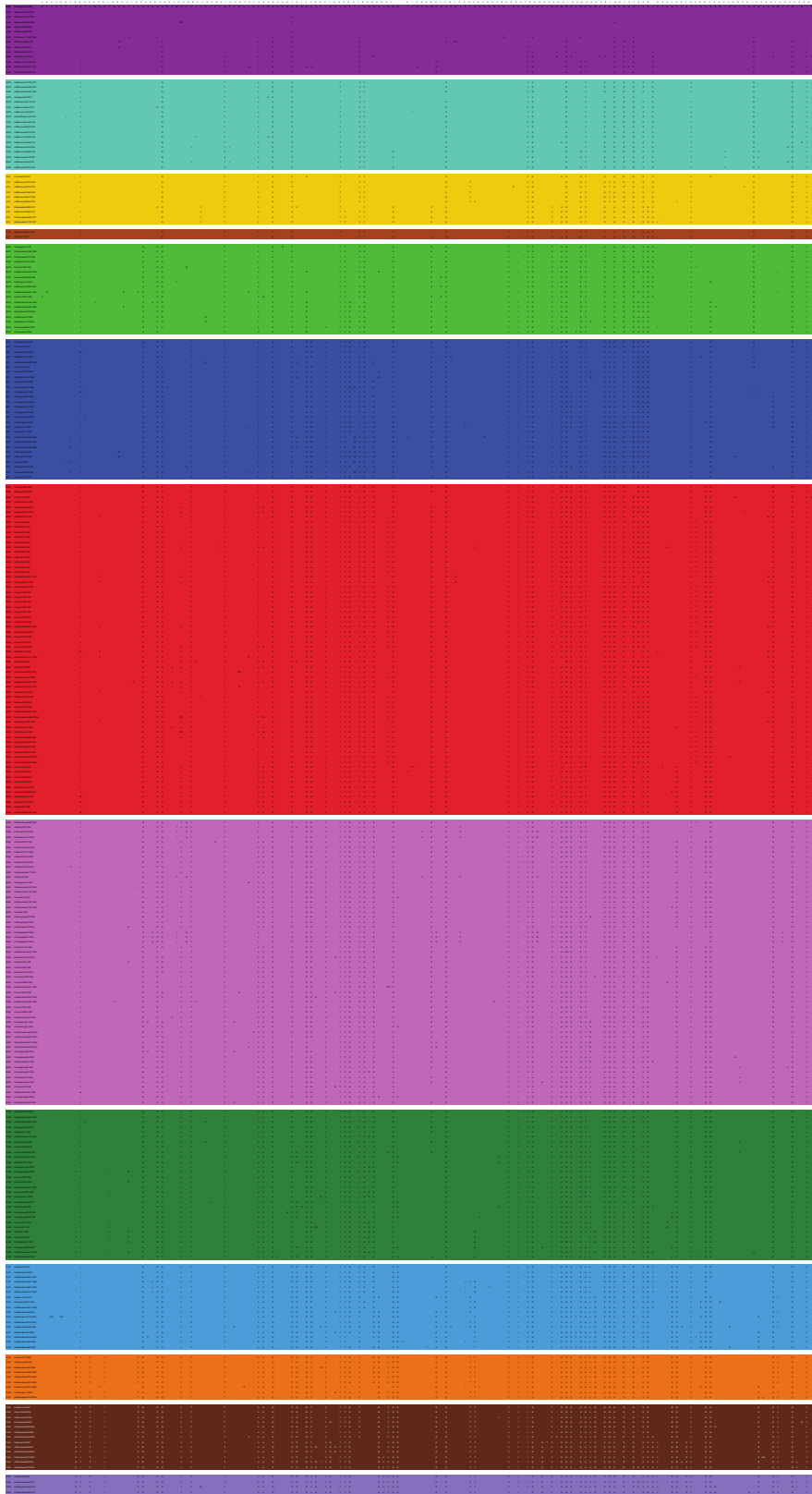


FIG S2F.

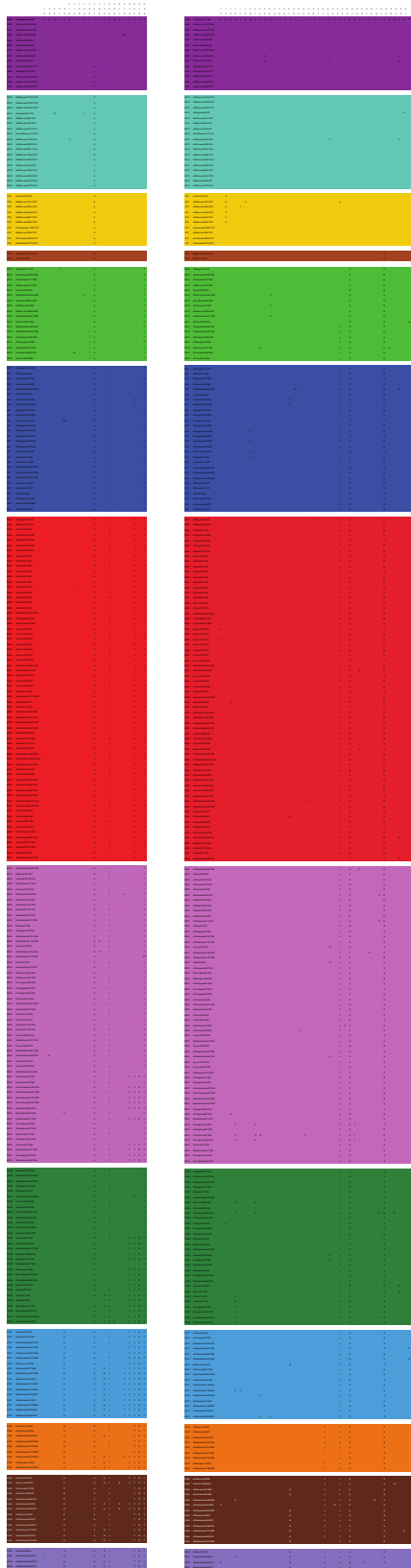


FIG S2G.

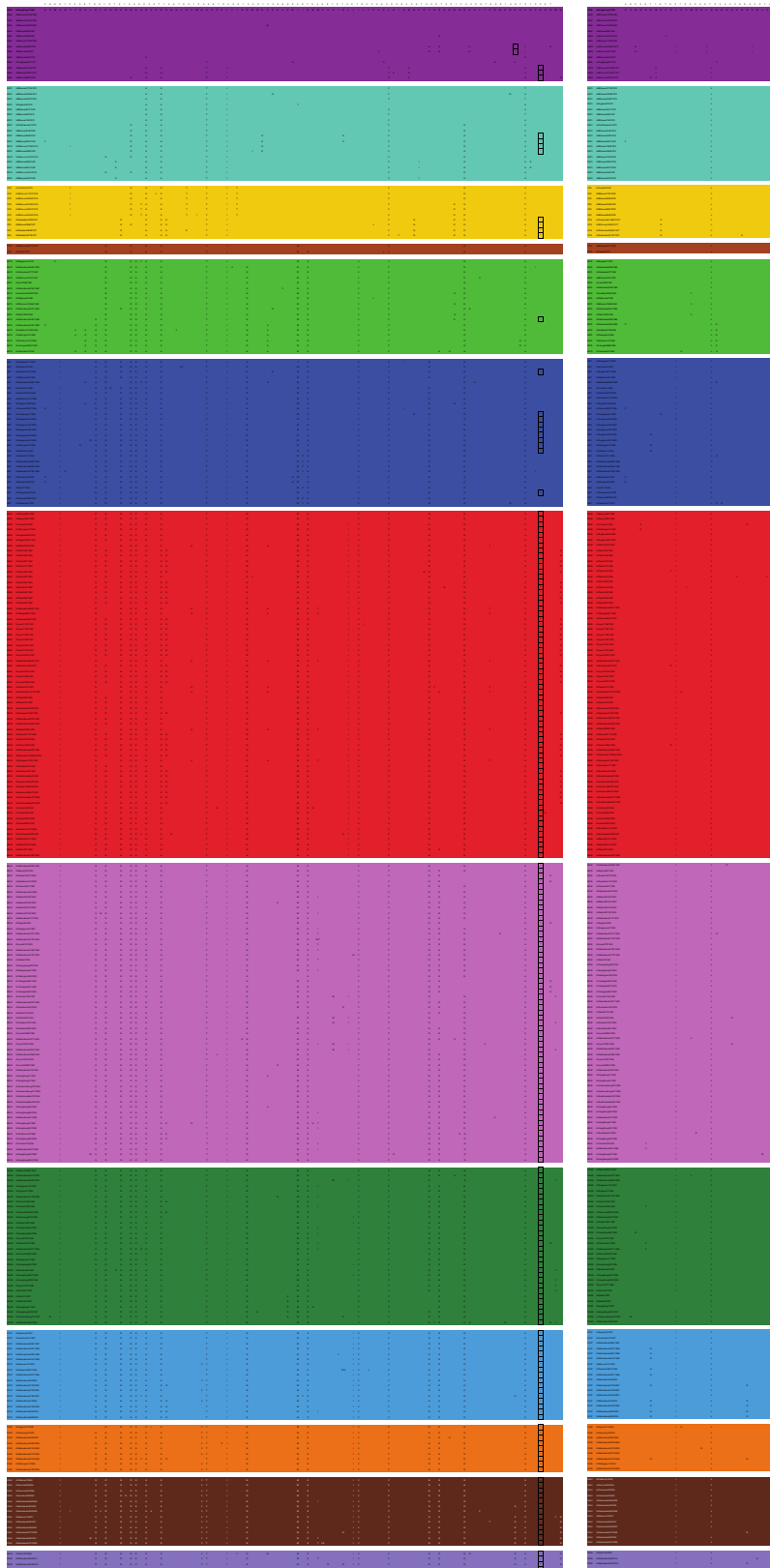


FIG S2H.

TABLE S1. The ORFs of A(H3N2) virus.

Segment	Gene	Length (bp)	ORF	Protein (length in aa)
1	PB2	2341	28..2307	PB2 (759)
			25..2298	PB1 (757)
2	PB1	2341	142..2298	PB1-N40 (718)
			119..391	PB1-F2 (90)
3	PA	2233	25..2175	PA (716)
			487..2175	PA-N155 (562)
			568..2175	PA-N182 (535)
			599..781	PA-X (61)
4	HA	1765	30..1730	HA (566)
5	NP	1566	46..1542	NP (498)
6	NA	1468	20..1429	NA (469)
7	MP	1027	26..784	M1 (252)
			26..51 join 740..1007	M2 (97)
8	NS	890	27..740	NS2 (237) ^a
			27..719	NS2 (230) ^b
			27..689	NS2 (220) ^c
			27..56 join 529..864	NS2 (121)

^a Circulating in 1968 - 1991

^b Circulating in 1971 - 2011

^c Circulating in 1970

bp, Base pair

aa, Amino acid

TABLE S2. Best-fit models of protein evolution based on the Akaike information criterion.

Segment	Length (aa)	Model	lnL
PB2	759	FLU+I+ Γ 4+F	-3588.624
PB1	757	FLU+I+ Γ 4+F	-3845.97
PB1-N40	718	FLU+I+ Γ 4+F	-3654.85
PB1-F2	90	HIVw+ Γ 4	-1344.21
PA	716	HIVb+I+ Γ 4+F	-3723.65
PA-N155	562	HIVb+I+ Γ 4+F	-2986.37
PA-N182	535	HIVb+I+ Γ 4+F	-2875.34
PA-X	61	HIVb	-390.45
HA0	566	HIVw+I+ Γ 4	-6634.43
HA1	329	HIVw+ Γ 4	-4830.01
HA2	121	HIVw+ Γ 4	-1252.39
NP	498	FLU+I+ Γ 4+F	-2614.41
NA	469	HIVw+I+ Γ 4+F	-4582.06
M1	252	FLU+I+F	-912.15
M2	97	HIVb+ Γ 4	-730.40
NS2	220	HIVw+ Γ 4	-1964.02
NS2	121	HIVw+ Γ 4+F	-663.324

HIVw, Human immunodeficiency virus within hosts

HIVb, Human immunodeficiency virus between hosts

FLU, Influenza-specific amino acid substitution model

Γ 4, Rate heterogeneity gamma distribution of among-site rate variation with four categories estimated from the empirical data

I, Proportion of invariable sites

F, unequal base frequencies

lnL, Log likelihood

TABLE S3. To test if the time of circulation of the MRCA of a gene segment (row) is significantly different from the time of circulation of the MRCA of other gene segments (column) of a given antigenic cluster, a Bayes factor test was performed* (3-7). The time of circulation of MRCAs are significantly different if the Bayes factor values are <0.11 and >9.0 (highlighted in bold).

Cluster		PB1	PA	HA	NP	NA	MP	NS
HK68	PB2	2.63	0.02	2.13	0.24	0.07	0.36	0.69
	PB1		0	0.69	0.06	0	0.10	0.18
	PA			> 100	11.07	5.05	15.52	57.71
	HA				0.08	0.01	0.12	0.27
	NP					0.37	1.47	3.03
	NA						4.16	9.85
	M							1.88
EN72	PB2	0.69	0.94	0.97	0.54	0.39	0.34	0.27
	PB1		0.79	0.62	0.41	0.28	0.20	0.11
	PA			0.53	0.30	0.14	0.09	0.05
	HA				0.26	0.11	0.08	0.04
	NP					0.35	0.24	0.19
	NA						0.35	0.25
	M							0.48
VI75	PB2	0.79	0.10	> 1000	0.06	0.28	> 100	0.04
	PB1		0.13	> 1000	0.07	0.41	> 100	0.03
	PA			> 1000	0.39	1.92	> 1000	0.42
	HA				> 100	0	0.08	0
	NP					4.22	> 1000	1.19
	NA						> 100	0.20
	M							0
TX77	PB2	1.14	1.81	0.50	1.29	2.38	2.05	2.41
	PB1		1.69	0.63	1.27	2.81	2.02	1.98
	PA			0.26	1.22	1.50	0.99	1.38
	HA				1.22	4.59	5.03	4.88
	NP					2.20	1.45	1.80
	NA						0.61	0.78
	M							1.20
BK79	PB2	2.92	0.75	1.11	0.22	0.34	0.31	0.32
	PB1		0.22	0.11	0.02	0.23	0.12	0.07
	PA			0.57	0.18	1.01	0.39	0.39
	HA				0.07	0.57	0.36	0.25

	NP					12.56	3.38	4.24
	NA						0.40	0.34
	M							1.04
SI87	PB2	1.74	1.10	46.19	0.39	0	0	0
	PB1		0.59	35.42	0.21	0	0	0
	PA			>100	0.42	0	0	0
	HA				0	0	0	0
	NP					0	0.01	0
	NA						1.00	0.75
	M							0.83
BE89	PB2	0.86	2.82	3.61	0.44	3.19	1.26	2.35
	PB1		3.35	3.62	0.52	4.60	1.56	2.33
	PA			1.58	0.22	1.36	0.49	1.11
	HA				0.16	0.82	0.35	0.85
	NP					7.60	2.48	3.39
	NA						0.39	0.78
	M							1.76
BE92	PB2	0.85	3.67	>1000	7.93	0.90	1.06	0.68
	PB1		4.83	>1000	9.21	1.32	1.32	0.66
	PA			>1000	6.32	0.31	0.32	0.27
	HA				0.11	0	0	0
	NP					0.11	0.13	0.12
	NA						0.97	0.59
	M							0.62
WU95	PB2	>1000	3.67	>1000	16.23	>1000	1.07	0.68
	PB1		0	>100	0	1.67	0	0
	PA			>1000	13.06	>1000	0.32	0.27
	HA				0	0.01	0	0
	NP					>100	0.07	0.06
	NA						0	0
	M							0.62
SY97	PB2	3.35	1.20	1.01	0.06	0	1.04	0.11
	PB1		0.38	0.23	0.01	0	0.44	0.03
	PA			0.89	0.05	0	0.82	0.09
	HA				0.05	0	0.91	0.10
	NP					0.12	9.93	1.15
	NA						78.30	3.81
	M							0.16
FU02	PB2	0.43	0.79	>1000	0	0.30	0.10	0.01
	PB1		1.75	>1000	0	0.72	0.16	0.01
	PA			>1000	0	0.45	0.10	0.01
	HA				0	0	0	0
	NP					1021.95	29.51	3.20

	NA						0.25	0.04
	M							0.28
CA04	PB2	0	0	3.59	0	4.41	0	0.73
	PB1		0.24	> 1000	0.68	> 1000	1.76	40.66
	PA			> 1000	2.75	> 1000	4.62	> 100
	HA				0	1.45	0	0.32
	NP					> 1000	2.29	63.15
	NA						0	0.25
	M							27.52
PE09	PB2	6.79	5.30	> 1000	8.89	24.14	23.32	1.04
	PB1		1.11	> 100	2.17	4.76	3.98	0.23
	PA			> 100	2.31	3.97	3.13	0.30
	HA				0.06	0.05	0.04	0
	NP					1.59	1.38	0.17
	NA						0.82	0.07
	M							0.09

*Bayes factor: $\frac{P(A>B|D)}{1-P(A>B|D)} \times \frac{1-P(A>B)}{P(A>B)}$

TABLE S4. Reassortment events between segments of human (A)H3N2 viruses circulating between 1968 and 2011 analyzed with GiRaF(8). Persistent reassortment events are shown in bold.

Event ^a	Isolates
1	A/Bilthoven/16190/1968
2	A/Bilthoven/93/1970, A/Bilthoven/2668/1970
3	A/Amsterdam/1609/1977, A/Bilthoven/3895/1977, A/Rotterdam/5828/1977, A/Rotterdam/8179/1977
4	A/Phillippines/2/1982
5*	A/Akita/4/1993, A/Lyon/672/1993, A/Netherlands/17/1993, A/Netherlands/3/1992, A/Shangdong/9/1993
6	A/Yamagata/56/1993
7	A/Lyon/22686/1993
8	A/Shangdong/9/1993
9	A/Akita/4/1993, A/Lyon/672/1993, A/Madrid/G102/1993, A/Madrid/G130/1993, A/Netherlands/101/1993, A/Netherlands/115/1993, A/Netherlands/126/1993, A/Shangdong/9/1993, A/Singapore/3/1993
10	A/Hong Kong/1/1994, A/Hong Kong/42/1996, A/Hong Kong/434/1996, A/Hong Kong/55/1994, A/Johannesburg/33/1994, A/Johannesburg/47/1994, A/Netherlands/1/1995
11*	A/Hong Kong/1/1994, A/Hong Kong/434/1996, A/Hong Kong/55/1994, A/Johannesburg/33/1994, A/Johannesburg/47/1994
12	A/Hong Kong/55/1995
13	A/Netherlands/1/1995
14*	A/Hong Kong/42/1996
15*	A/Akita/4/1993, A/Auckland/10/1997, A/Brisbane/10/2007, A/Brisbane/8/1996, A/California/7/2004, A/England/7/1994, A/Finland/247/1992, A/Finland/338/1995, A/Finland/339/1995, A/Finland/381/1995, A/Fujian/411/2002, A/Geneva/3958/1996, A/Geneva/A9509/1995, A/Guangdong/25/1993, A/Hiroshima/52/2005, A/Hong Kong/1/1994, A/Hong Kong/1/1997, A/Hong Kong/2/1994, A/Hong Kong/20/1996, A/Hong Kong/280/1997, A/Hong Kong/3/1995, A/Hong Kong/32/1995, A/Hong Kong/357/1996, A/Hong Kong/358/1996, A/Hong Kong/38/1995, A/Hong Kong/42/1996, A/Hong Kong/434/1996, A/Hong Kong/49/1995, A/Hong Kong/55/1994, A/Hong Kong/55/1995, A/Hong Kong/56/1994, A/Johannesburg/10/1997, A/Johannesburg/33/1994, A/Johannesburg/47/1994, A/Lyon/1781/1996, A/Lyon/1803/1993, A/Lyon/1815/1993, A/Lyon/22686/1993, A/Lyon/2279/1995, A/Lyon/23602/1993, A/Lyon/672/1993, A/Madrid/G102/1993, A/Madrid/G109/1993, A/Madrid/G122/1993, A/Madrid/G130/1993, A/Madrid/G252/1993, A/Moscow/10/1999, A/Nanchang/933/1995, A/Netherlands/1/1995, A/Netherlands/1/2002, A/Netherlands/101/1993, A/Netherlands/115/1993, A/Netherlands/118/2001, A/Netherlands/120/2002, A/Netherlands/124/2001, A/Netherlands/126/1993, A/Netherlands/126/2001, A/Netherlands/132/2004, A/Netherlands/17/1993, A/Netherlands/178/1995, A/Netherlands/179/1993, A/Netherlands/18/1994, A/Netherlands/20/2003, A/Netherlands/213/2003, A/Netherlands/217/2003, A/Netherlands/22/2003, A/Netherlands/222/2003, A/Netherlands/241/1993, A/Netherlands/271/1995, A/Netherlands/3/1992, A/Netherlands/3/2000, A/Netherlands/300/1997, A/Netherlands/301/1999, A/Netherlands/312/2003, A/Netherlands/34/2010, A/Netherlands/348/2007, A/Netherlands/357/1993, A/Netherlands/363/2006, A/Netherlands/371/1993, A/Netherlands/372/1993, A/Netherlands/377/2008, A/Netherlands/398/1993, A/Netherlands/399/1993, A/Netherlands/414/1999, A/Netherlands/42/2006, A/Netherlands/427/1998, A/Netherlands/462/1998, A/Netherlands/5/1998, A/Netherlands/548/2008, A/Netherlands/55/2004, A/Netherlands/63/2011, A/Netherlands/69/2007, A/Netherlands/69/2009, A/Netherlands/761/2009, A/Netherlands/88/2003, A/Netherlands/9/2010, A/Netherlands/91/1996, A/Nice/491/1997, A/Oslo/21/1997, A/Oslo/2219/1993, A/Oslo/2352/1993, A/Oslo/244/1997, A/Panama/2007/1999, A/Perth/16/2009, A/Scotland/142/1993, A/Scotland/160/1993, A/Shangdong/9/1993, A/Singapore/1/1996, A/Singapore/19/1993, A/Singapore/3/1993, A/South Australia/15/1994, A/South Australia/25/1994, A/Stockholm/20/1993, A/Stockholm/5/1995, A/Sydney/5/1997, A/Victoria/104/1993, A/Victoria/75/1995, A/Wellington/1/2004, A/Wellington/59/1993, A/Wisconsin/67/2005, A/Wuhan/359/1995, A/Wyoming/3/2003
16*	A/Akita/4/1993, A/Auckland/10/1997, A/Brisbane/10/2007, A/Brisbane/8/1996, A/California/7/2004, A/Finland/247/1992, A/Finland/338/1995, A/Finland/339/1995, A/Finland/381/1995, A/Fujian/411/2002, A/Geneva/3958/1996, A/Geneva/A9509/1995, A/Guangdong/25/1993, A/Hiroshima/52/2005, A/Hong Kong/1/1994, A/Hong Kong/1/1997, A/Hong Kong/2/1994, A/Hong

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20*	A/Lyon/1803/1993, A/Netherlands/357/1993, A/Netherlands/399/1993, A/Oslo/2352/1993, A/Scotland/142/1993, A/Victoria/104/1993
21*	A/Netherlands/357/1993, A/Netherlands/399/1993, A/Scotland/142/1993, A/Victoria/104/1993
22*	A/England/7/1994, A/Lyon/1803/1993, A/Lyon/1815/1993, A/Lyon/22686/1993, A/Lyon/23602/1993, A/Netherlands/18/1994, A/Netherlands/241/1993, A/Netherlands/357/1993, A/Netherlands/371/1993, A/Netherlands/372/1993, A/Netherlands/398/1993, A/Netherlands/399/1993, A/Oslo/2352/1993, A/Scotland/142/1993, A/Scotland/160/1993, A/Stockholm/20/1993, A/Victoria/104/1993
23*	A/England/7/1994, A/Lyon/1815/1993, A/Lyon/22686/1993, A/Lyon/23602/1993, A/Netherlands/18/1994, A/Netherlands/241/1993, A/Netherlands/371/1993, A/Netherlands/372/1993, A/Netherlands/398/1993, A/Scotland/160/1993, A/Singapore/19/1993, A/Stockholm/20/1993
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26	A/Akita/4/1993, A/Finland/338/1995, A/Finland/339/1995, A/Geneva/A9509/1995, A/Guangdong/25/1993, A/Hong Kong/2/1994, A/Hong Kong/20/1996, A/Hong Kong/3/1995, A/Hong Kong/32/1995, A/Hong Kong/38/1995, A/Hong Kong/49/1995, A/Hong Kong/55/1995, A/Hong Kong/56/1994, A/Lyon/672/1993, A/Madrid/G109/1993, A/Madrid/G122/1993, A/Madrid/G252/1993, A/Nanchang/933/1995, A/Netherlands/115/1993, A/Netherlands/126/1993, A/Netherlands/178/1995, A/Netherlands/179/1993, A/Oslo/2219/1993, A/Shangdong/9/1993, A/Stockholm/5/1995, A/Wellington/59/1993, A/Wuhan/359/1995
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36	A/Lyon/2279/1995
37*	A/Hong Kong/20/1996, A/Nanchang/933/1995, A/Wuhan/359/1995
38	A/Brisbane/8/1996

39	A/Hong Kong/20/1996
40*	A/Geneva/3958/1996, A/Lyon/1781/1996, A/Nice/491/1997, A/Singapore/1/1996
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43*	A/Hong Kong/1/1997, A/Hong Kong/280/1997, A/Johannesburg/10/1997, A/Oslo/21/1997, A/Oslo/244/1997
44*	A/Hong Kong/1/1997, A/Johannesburg/10/1997, A/Oslo/21/1997, A/Oslo/244/1997
45	A/Hong Kong/1/1997, A/Hong Kong/280/1997, A/Johannesburg/10/1997, A/Netherlands/5/1998, A/Oslo/21/1997, A/Oslo/244/1997
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47*	A/Netherlands/5/1998
48	A/Auckland/10/1997, A/Brisbane/10/2007, A/Brisbane/8/1996, A/California/7/2004, A/Fujian/411/2002, A/Hiroshima/52/2005, A/Hong Kong/280/1997, A/Hong Kong/357/1996, A/Hong Kong/358/1996, A/Hong Kong/42/1996, A/Lyon/2279/1995, A/Moscow/10/1999, A/Netherlands/1/2002, A/Netherlands/118/2001, A/Netherlands/120/2002, A/Netherlands/124/2001, A/Netherlands/126/2001, A/Netherlands/132/2004, A/Netherlands/20/2003, A/Netherlands/213/2003, A/Netherlands/217/2003, A/Netherlands/22/2003, A/Netherlands/222/2003, A/Netherlands/3/2000, A/Netherlands/300/1997, A/Netherlands/301/1999, A/Netherlands/312/2003, A/Netherlands/34/2010, A/Netherlands/348/2007, A/Netherlands/363/2006, A/Netherlands/377/2008, A/Netherlands/414/1999, A/Netherlands/42/2006, A/Netherlands/427/1998, A/Netherlands/462/1998, A/Netherlands/5/1998, A/Netherlands/548/2008, A/Netherlands/55/2004, A/Netherlands/63/2011, A/Netherlands/69/2007, A/Netherlands/69/2009, A/Netherlands/761/2009, A/Netherlands/88/2003, A/Netherlands/9/2010, A/Panama/2007/1999, A/Perth/16/2009, A/Sydney/5/1997, A/Wellington/1/2004, A/Wisconsin/67/2005, A/Wyoming/3/2003
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52	A/Netherlands/126/2001
53	A/Netherlands/124/2001, A/Netherlands/3/2000
54*	A/Netherlands/312/2003
55*	A/Brisbane/10/2007, A/California/7/2004, A/Fujian/411/2002, A/Hiroshima/52/2005, A/Netherlands/132/2004, A/Netherlands/213/2003, A/Netherlands/217/2003, A/Netherlands/22/2003, A/Netherlands/34/2010, A/Netherlands/348/2007, A/Netherlands/363/2006, A/Netherlands/377/2008, A/Netherlands/42/2006, A/Netherlands/548/2008, A/Netherlands/55/2004, A/Netherlands/63/2011, A/Netherlands/69/2007, A/Netherlands/69/2009, A/Netherlands/761/2009, A/Netherlands/9/2010, A/Perth/16/2009, A/Wellington/1/2004, A/Wisconsin/67/2005, A/Wyoming/3/2003
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57*	A/Netherlands/363/2006

58*	A/Brisbane/10/2007, A/Hiroshima/52/2005, A/Netherlands/34/2010, A/Netherlands/348/2007, A/Netherlands/377/2008, A/Netherlands/548/2008, A/Netherlands/63/2011, A/Netherlands/69/2007, A/Netherlands/69/2009, A/Netherlands/761/2009, A/Netherlands/9/2010, A/Perth/16/2009, A/Wisconsin/67/2005
59	A/Brisbane/10/2007, A/Netherlands/34/2010, A/Netherlands/348/2007, A/Netherlands/377/2008, A/Netherlands/63/2011, A/Netherlands/69/2007, A/Netherlands/69/2009, A/Netherlands/761/2009, A/Netherlands/9/2010, A/Perth/16/2009

^a Event numbering corresponds to Fig. 2.

* Events involving HA are depicted as bold twines in the tanglegrams (Fig. 2)

TABLE S5. Positively selected sites within all ORFs selected by IFEL, MEME, FUBAR, and DEPS. The images can be zoomed to show details.

ORF	Codon	Location	Antigenic site	Amino Acid	Year	Antigenic cluster	IFEL ⁹	MEME ²	FUBAR ³	DEPS ¹⁰
PB2	553	Cap binding (9, 10) NP interaction (9, 10) RNA binding (11)		I	1968-2011	All			√	√ (I)
	697	PB1 interaction (9, 10) NP interaction (9, 10) Importin binding (11)		V	1989-1996	S187-WU95				
				L	1968-1996	H68-WU95				
PB1	633	PB1 interaction (9, 10) PB1-N40		I	1995-2011	BE92-PE09				√ (I)
				S	1968-2011	All		√		
PB1-F2	23			T	1994	BE92				
				S	1968-2011	All				
	90			N	1969, 1972, 1977, 1986, 1989, 1990, 1992, 1995, 1996	HK68, TX77, BK79, S187, BE89, WU95				√ (N)
				D	1977	VI75				
	87	Endonuclease domain (11)		G	1968-1975, 1977, 2005	HK68-TX77				√ (N)
				N	1975, 1976, 1979-2011	EN72-PE09				
	277	PB1 binding (11) PA-N155/PA-N182		A	1968-2011	All			√	
				G	1989	S187				
				F	1968-1985, 1993, 2001	H68-BK79, BE92, SY97				
				Y	1985-1989	BK79-PE09			√	
PA	311	PB1 binding (11) PA-N155/PA-N182		H	1989	S187				
				M	1968-1986, 1988-1991, 1993, 1995, 2004, 2005, 2007	HK68-S187, BE92, WU95, FU02, CA04				
	437	PB1 binding (11) PA-N155/PA-N182		I	1987-2011	S187-PE09				√ (M)
				V	1995	WU95				
	486	PB1 binding (11) PA-N155/PA-N182		Y	1968-2004, 2006	HK68-CA04			√	
			H	1995-1997, 2005-2011	BE92-PE09					
HA*	549	PB1 binding (11) PA-N155/PA-N182		I	1968-2011	All			√	
				V	1988	S187				
	11			L	1968-2011	All			√	
				F	1968-1991	HK68-S187				
	12			L	1981, 1982, 1989-2011	BK79-PE09				√ (L)
				S	1985	BK79				
				C	1968-2011	All				
	47	HA1 [81]		Y	1971	HK68			√	
				H	1993	BE92				
				R	2010	PE09				
79	HA1 [63]		D	1968, 1970-1975	HK68, EN72				√ (N)	
			N	1968-1970, 1973-2011	All					
95	HA1 [79]		F	1968-2011	All				√ (L)	
			L	1975, 1990, 1992, 1994	EN72, S187-BE92					
128	HA1 [112]		V	1968-2011	All			√		
			I	1970, 1980, 2003, 2006, 2009	HK68, BK79, FU02, CA04					
			I	1968-1994, 1996	HK68-WU95					
137	HA1 [121]		T	1969, 1983, 1990-1993, 1995-1998	HK68, BK79-WU95			√	√ (T)	
			N	1996-2011	WU95-PE09					
149	HA1 [133]		N	1968-1977, 1992, 1993, 1996-2011	HK68-TX77, BE89, WU95-PE09					
			S	1979-1993	BK79-BE89			√		
HA*	151	HA1 [135]		D	1992-1998	BE92-WU95				
				G	1968-1993	HK68-S187, BE92, WU95				
	153	HA1 [137]		E	1989-1992	BE89				
				G	1992	BE89			√	√
				D	1991-1993	BE89				
				K	1993-1996	BE92, WU95				
	154	HA1 [136]		T	1985-2011	WU95-PE09				
				N	1968	HK68				
	155	HA1 [137]		I	1971	HK68				
				S	1971, 1972, 1976, 1977, 1982, 1998-2011	HK68-VI75, BK79, SY97-PE09				
161	HA1 [145]		Y	1976-1986, 1988-1998	TX77-SY97		√	√	√	√ (S)
			G	1977	VI75					
160	HA1 [144]		H	1987	S187					
			C	1987, 1993	S187, BE92					
161	HA1 [145]		A	1968-2011	All					
			T	1982, 1991, 1993, 1998	BK79-WU95			√	√	√ (ST)
			S	1986, 1993, 1995, 2004, 2005, 2008	BK79, BE92, WU95, CA04					
			G	1968-1972	HK68					
171	HA1 [155]		D	1971-1983, 2002, 2003, 2006	HK68-BK79, SY97, CA04					
			N	1982, 1999, 2001-2010	BK79, SY97-PE09					
			V	1985-1998	BK79-WU95				√	
			I	1997, 1998, 2000	SY97					
161	HA1 [145]		K	2009, 2011	PE09					
			I	1968, 1971, 1974, 1975	HK68-VI75					
			S	1968-1975	HK68, EN72					
			N	1973, 1976-1996, 2004-2011	EN72-S187, BE92, CA04, PE09		√	√	√	√ (IK)
171	HA1 [155]		C	1974	EN72					
			R	1974, 1975	EN72					
			K	1977, 1979, 1988-2004	VI75, BK79-FU02					
			T	1968-1972, 2002-2011	HK68, FU02-PE09					

			K	1968-1977, 1985, 1989-1998	HK68-SI87, BE92, WU95				
			E	1979-1993	BK79-BE89				√ (K)
172	HA1 [156]	B (12, 13)	H	2002-2011	FU02-PE09				
			C	1997-2003, 2005	SY97, CA04				
			G	1968-1977	HK68-VI75				
			E	1976-1998	TX77-WU95				
			C	1991	SI87				
174	HA1 [156]	B (12, 13)	D	1991, 1992, 1995, 1996	BE89, BE92				√
			K	1997-2009	SY97-CA04				
			N	1999, 2009-2011	SY97, PE09				
			R	2003, 2009	SY97, CA04				
			S	1968	HK68				
			R	1971	HK68				
175	HA1 [159]	B (12, 13)	N	1974, 1975, 2003	EN72, SY97	√	√	√	√ (Q)
			Y	1985-2003	BK79-FU02				
			C	1987	SI87				
			F	1995, 2004-2011	WU95, FU02-PE09				
			D	1968-1977, 1991-1993, 1995-1998	HK68-TX77, BE89-SY97				
188	HA1 [172]	D (12, 13)	G	1979-1996	BK79-WU95	√			
			E	1999-2011	SY97-PE09				
			H	1968-2011	All				
199	HA1 [183]		L	2002, 2005, 2006, 2009	FU02-PE09				√ (L)
			S	1968	HK68-				
			I	1966, 1987	BK79, SI87				
202	HA1 [186]	B (12, 13)	G	2001-2011	SY97-PE09				√ (V)
			V	2003-2005	FU02, CA04				
			S	1968-1975, 1990-2004, 2006	HK68, EN72, SI87-CA04				
			N	1971, 1973-1991	HK68, EN72, TX77-SI87				
			D	1975-1977	VI75	√	√	√	
HA* (cont.)	209	HA1 [193]	B (12, 13)	K	1982, 1989	BK79, BE89			
			R	2004	CA04				
			F	2005-2011	CA04, PE09				
			L	1968-2011	All				
	210	HA1 [194]	B (12, 13)	I	1994, 1995, 1997, 1999	BE92-SY97			√ (I)
			P	2007	CA04				
			A	1968	HK68				
			T	1971, 1973	HK68, EN72				
	214	HA1 [196]	B (12, 13)	S	1996, 1999, 2010	BE92-SY97, PE09			√ (S)
			E	2004	FU02				
			I	1968-1981	HK68-BK79				
	229	HA1 [213]	D (12, 13)	V	1975-1977, 1982-2011	EN72, VI77, BK79-PE09			√ (V)
			M	1968	HK68				
			L	1968-1996	HK68-WU95				
	242	HA1 [226]	D (12, 13)	Q	1970, 1990, 1992-1994, 1996	HK68, SI87, BE92, WU95	√	√	√ (Q)
			P	1972	HK68				
			I	1994-1997, 2003-2011	BE92-PE09				
			V	1995-2003	WU95-FU02				
			R	1968-1976, 1980-2011	HK68-PE09				
	245	HA1 [229]	D (12, 13)	G	1975, 1977, 1979, 1989, 1993, 1998	EN72, TX77-SI87, BE92, SY97			√
			G	1996, 1998	WU95, SY97				
			T	1968	HK68				
			N	1976, 1982, 1983, 1987, 1990, 1992-1996	TX77-SI87, BE92, WU95				
	278	HA1 [262]	E (12)	I	1991	BE89			√
			S	1995-2011	WU95-PE09				
			A	1968-2011	All				
	320	HA1 [304]	C (12, 13)	P	1994, 1997	BE92, WU95			√
			I	1968-2011	All				
	538	HA2 [193], TM anchor	T	1989, 1994, 1995, 2001	SI87, BE92-SY97				√ (T)
			M	2004	FU02				
	54	RNA binding site (9, 10)	G	1968-2011	All			√	
		PB2 interaction (9)	A	1972	HK68				
NP	146	RNA binding site (9, 10)	T	1968-2001	HK68-SY97			√	
		PB2 interaction (9)	A	1975, 1977, 1988, 2001-2011	EN72, VI75, SI87, SY97-PE09				
			D	1968-1977	HK68-TX77				
	43	Stalk	S	1979-1993, 1997, 2006	BK79-SI87, BE92, SY97, CA04	√	√		
			N	1998-2011	BE88-PE09				
			A	1968	HK68-TX77				
	46	Stalk	S	1969	HK68				√ (P)
			P	1973, 1977, 1979-2011	EN72, VI75, BK79-PE09				
			P	1968-1993	HK68-BE92				
NA	52	Stalk	L	1969, 1991-2011	HK68, BE89-PE09				√ (L)
			I	1968-1986, 1988	HK68-SI87				
	56	Stalk	T	1975, 1987-2011	EN72, SI87-PE09				√ (K)
			K	1992, 1993, 2001	BE89, BE92, SY97				
			G	1968	HK68-WU95				
	127	Head	S	1977, 1988, 1989, 1992	VI75, SI87, BE89, BE92				√ (S)
			D	1988, 1995-2010	SI87, WU95-PE09				
			N	2011	PE09				

			T	1968-2011	A		
148	Head		E	1996	WU95	√	
			I	1996	WU95		
			K	2001	SY97		
199	Head	B (12, 13)	K	1968-1989, 2003-2011	HK68-SI87, SY97-PE09		
			E	1971, 1989-2003	HK68, SI87-FU02	√	
			D	1988	SI87		
253	Head		R	1968-1972	HK68, EN72		√ (K)
			K	1970, 1972-2011	HK68, EN72-PE09		
			P	1968-2000	HK68-WU95		
			S	1976, 1992	VI75, BE89		
			Q	1997, 1998	WU95, SY97		
267	Head		K	1999	SY97		√
			T	2001-2011	SY97-PE09		
			L	2001	SY97		
			S	2001	SY97		
308	Head		E	1968-1970	HK68		√ (K)
			K	1969-2011	HK68-PE09		
328	Head	C (12, 13)	N	1968-1976, 1992	HK68-TX77, BE89		√ (K)
			K	1974, 1975, 1977-2011	EN72-PE09		
			N	1968-1975	HK68, EN72		
334	Head	C (12, 13)	K	1969	HK68		√ (S)
			S	1971, 1975-2011	HK68-PE09		
			R	1968-1994	HK68-WU95		
338	Head	C (12, 13)	Q	1985, 1988, 1994	BK79, SI87, BE92	√	
			L	1992, 1994-2011	BE89-PE09		
			W	1993-1996	BE92		
339	Head	C (12, 13)	N	1968-1999	HK68-SY97		√
			K	1993	BE92		
			D	1997, 1999-2011	WU95-PE09		
			L	1968-1970, 1982, 1985-2006	HK68, BK79-CA04		
370	Head	C (12, 13)	S	1971-1983, 1995, 1997, 1998, 2006-2011	HK68-BK79, BE92-SY97, CA04, PE09	√	√ (S)
			F	1997, 1998	SY97		
			S	1968-2006	HK68-CA04		
372	Head		L	1977, 1996, 1992, 1993, 2007-2011	VI75, BK79, BE89, BE92, CA04, PE09		√ (L)
			D	1968-1983, 1998	HK68-BK79, SY97		
			A	1975	VI75		
401	Head	A (12, 13)	G	1982, 1985, 1987-1997, 1999-2011	BK79, SI87-PE09	√	
			K	1985, 1986, 1988	BK79, SI87		
			S	1993	BE92		
437	Head		W	1968-2003	HK68-FU02		√ (L)
			L	1982, 1999-2011	BK79, SY97-PE09		
465	Head		N	1968	A		√
			D	1974	EN72		
			G	2005	CA04		
M1	166	C-terminal domain (11)	V	1968-1985, 1987-2011	A	√	
			I	1985, 1986, 1989	BK79, SI87		
			A	1968	A		
			T	1976, 1979, 1988, 2001, 2003	VI75, BK79, SI87, SY97, FU02		√ (T)
58	dsRNA binding (11)		V	1993	BE89		
			S	1995	WU95		
65	dsRNA binding (11)		V	1968-2011	A	√	
			L	1976	VI75		
			E	1968-2011	A		
NS1	71	dsRNA binding (11)	K	1977, 1995	VI75, BE92, WU95	√	
			D	1991, 1992	BE89		
			G	2001-2003	SY97, FU02		
84	Effector domain (11)		A	1968-1971	HK68		√ (T)
			T	1971-2011	A		
			M	1968-2011	A		
129	Effector domain (11)	TCE 122-130 (15)	T	1991-1993, 1995, 2009, 2010	BE89, BE92, CA04, PE09		√ (T)
			I	1993-1996, 2003, 2008	BE92-SY97, CA04		

^a P<0.05

^b Posterior probability of ≥ 0.9

^c Bayes Factor > 20

^d The preferred residue(s) is/are indicated in parentheses.

* Location HA1/HA2 numbering is indicated between brackets.

TCE, T-cell epitope

dsRNA, double stranded RNA

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