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Full Length Research Paper

Novel characteristics and polymorphisms of hemagglutinin subunit 1 of 2009-2011 A/H1N1 viruses in Zhejiang, China

Yanjun Zhang, Haiyan Mao, Yin Chen, Jian Gao, Yiyu Lu, Zhen Li, Min Zhou, Liming Cong* and Lei Zhang*

Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, Zhejiang 310051, P. R. China.

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Since the 2009 pandemic A/H1N1 influenza virus emerged in North American, two H1N1 peaks have been reported in Zhejiang, China. The first peak occurred in November 2009 and the second in January 2011. In this study, we collected and analyzed the HA1 sequences of the Zhejiang H1N1 viruses in 2009 and 2010-2011. The phylogenic tree of HA1 suggested that the Zhejiang viruses were all derived from the 2009 pandemic viruses in North American. The consensus informational spectrum (CIS) of HA1 showed that the receptor binding preference of the Zhejiang viruses was also the same as that of the North American viruses. However, a lot of mutations in HA1 happened during local transmission and some of them could significantly increase or decrease the amplitude at the dominant frequency in informational spectrum (IS), implying that they may influence the receptor binding affinity. The structure analysis showed that four critical mutations, K219I, D222G, G225R and A134T, occurred in the receptor binding sites, among which D222G may be essential for the emergence of a lethal strain.

Key words: Influenza, H1N1, Hemagglutinin, information spectrum, Zhejiang.

INTRODUCTION

The majority of influenza epidemics are caused by influenza virus type A, which is coded by a genome of eight single-strand RNA segments (HA, NA, NP, M, NS, PA, PB1 and PB2) (Poland et al., 2007). Influenza A viruses can be further classified into different subtypes (H1N1, H2N2, H3N2, etc) based on the viral surface proteins hemagglutinin (HA) and neuraminidase (NA). HA is a spike-shaped homotrimer, where each monomer consists of two disulfide-linked subunits HA1 and HA2 (Mineev et al., 2013). HA1, which is at the distal end of the spike, is responsible for binding of the virus to its host cell receptors. HA2 forms the stem of the spike and mediates the fusion between the viral envelop and the host cell membrane (Skehel and Wiley, 2000). During the evolution of influenza viruses, their genome segments underwent continuous reassortments among different hosts including birds, pigs and humans (Zimmer and Burke, 2009). Influenza pandemics occur when newly emerged viruses are effectively transmit to the human population with no existing immunity.

In April 2009, a novel swine-origin influenza virus (pandemic 2009 A/H1N1) infected humans in North American and rapidly spread worldwide by human-to-human transmission. Up to April 2010, it is estimated that about 61 million people were infected with 2009 H1N1 and 12 thousand deaths occurred (Glatman-Freedman et al., 2012). Molecular phylogenic analyses revealed that the 2009 H1N1 virus was derived from several viruses reassorting in swine (Garten et al., 2009; Smith et al., 2009). The informational spectrum method (ISM) showed

*Corresponding authors. E-mail: Lmcong@cdc.zj.cn; lzhang@cdc.zj.cn. Tel: +86-571-87115198; +86-571-87115206. Fax: +86-571-87115198; +86-571-87115198.

that HA1 of the new virus has distinct biochemical characteristics from other H1N1 subtypes, which could reflect its receptor binding specificity (Veljkovic et al., 2009; Hu, 2010). The 3D structure of HA of the pandemic virus was also determined, which is similar to other reported HA structures but has a strict preference for human receptors (Xu et al., 2010; Yang et al., 2010).

In Zhejiang, China, the 2009 H1N1 virus was first reported in May. The percentage of sentinel respiratory specimens testing positive for H1N1 rapidly rose to 100% in November 2009. The second peak came in January 2011, but it was much lower than the first one. To understand the characteristics and variations of the H1N1 viruses in Zhejiang during 2009-2011, we collected and analyzed their HA1 sequences in this study.

METHODS

Sequence collection

The HA sequences of 2009 H1N1 viruses in Zhejiang were downloaded from the NCBI Influenza Virus Resource (http://www.ncbi.nlm.nih.gov/genomes/FLU) (Bao et al., 2008) among which A/Zhejiang-Yiwu/11/2009 is a lethal strain. In addition, we sequenced 20 H1N1 strains in Zhejiang during 2010-2011 (Supplementary Figure 1).

After collapsing identical sequences and excluding sequences with ambiguous nucleotides, we preserved 27 and 16 HA sequences in year 2009 and 2010-2011, respectively. The HA1 segments of the sequences were extracted by the NCBI Influenza Virus Sequence Annotation Tool (Bao et al., 2007). Based on a recent study, we also retrieved five representative HA1 sequences for each H1N1 subtype from NCBI, including American avian, Eurasian swine, American swine, human seasonal and 2009 American pandemic viruses.

Phylogeny construction

All HA1 sequences were aligned at the codon level by ClustalX 2.0.10 (Larkin et al., 2007). The phylogenic tree was constructed with the maximum likelihood (ML) method by MEGA 5.0.1 (Tamura et al., 2011). The substitution model were determined as GTR+I+Γ_4 (the general time-reversible model with the proportion of invariants sites and the gamma distribution of among-site rate variation with four categories) by jModelTest 0.1.1 (Posada et al., 2008). The robustness of the tree topology was evaluated with the bootstrap resampling method for 100 times.

Information spectrum method

The information spectrum method (ISM) for digital signal processing is widely used to identify the structural and functional characteristics of proteins (Veljkovic et al., 2008). Firstly, the amino acid sequence was translated to a numeric sequence according to the value of electron-ion interaction potential (EIIP), which represents the unique biophysical property of each amino acid (Godzik, 2003). Next, the numeric sequence is decomposed by discrete Fourier transform into a series of periodical functions. Finally, the informational spectrum (IS) for the sequence is computed as the energy density spectrum:

$$S(n) = |X(n)|^2 \quad (n = 1, 2, ...N/2)$$

Where, N is the sequence length, $X(n)$ is the discrete Fourier transformation coefficient and $S(n)$ is the amplitude at frequency n/N. The maximum frequency in IS is 0.5. The common frequency components for K amino acid sequences can be determined by their consensus informational spectrum (CIS):

$$C(n) = \prod_{i=1}^{K} S_i(n)$$

Where, $S_i(n)$ is the amplitude at frequency n/N for sequence i, and $C(n)$ is the corresponding amplitude in CIS. Generally speaking, the peak frequency in IS and CIS represents the primary biochemical property of proteins. The significance of a peak can be measured by its signal-to-noise ratio (S/N), which is defined as the ratio between its amplitude and the mean amplitude of the whole spectrum. We implemented the ISM algorithm in R.

Structure analysis

The crystal structure of the HA protein from the A/California/04/2009 H1N1 virus was retrieved from the RCSB PDB website (PDB ID: 3LZG). A HA1 monomer was extracted from the whole protein. The positions of individual amino acids were marked and displayed in the 3D structure by Jmol 12.2.

RESULTS

Phylogeny of HA1

We constructed the phylogenic tree for the representative HA1 sequences of H1N1, including those collected in Zhejiang during 2009-2011 (Figure 1). The phylogenic tree is consistent with previous reports, suggesting that the HA1 segments of the 2009 pandemic H1N1 viruses originated from the North American swine lineage. The 2009-2011 Zhejiang viruses are all grouped into the 2009 pandemic cluster, indicating that this subtype of viruses have undergone local transmission since they were imported in 2009.

Characteristics of informational spectrum

It has been demonstrated that the informational spectrums (IS) of HA1 of different H1N1 subtypes have different peak frequencies, which could characterize their receptor recognition preferences. Following the studies, we constructed the consensus informational spectrum (CIS) for HA1 of the 2009-2011 Zhejiang viruses, taking other H1N1 subtypes as control (Figure 2). The peaks of 2009 pandemic viruses are at the frequency F(0.086), while the peaks of swine and human seasonal viruses are at F(0.285) and F(0.058), respectively. The CIS of 2010-2011 Zhejiang viruses is quite similar to that of 2009, suggesting that HA1 did not have significant switches in receptor recognition during local transmission.

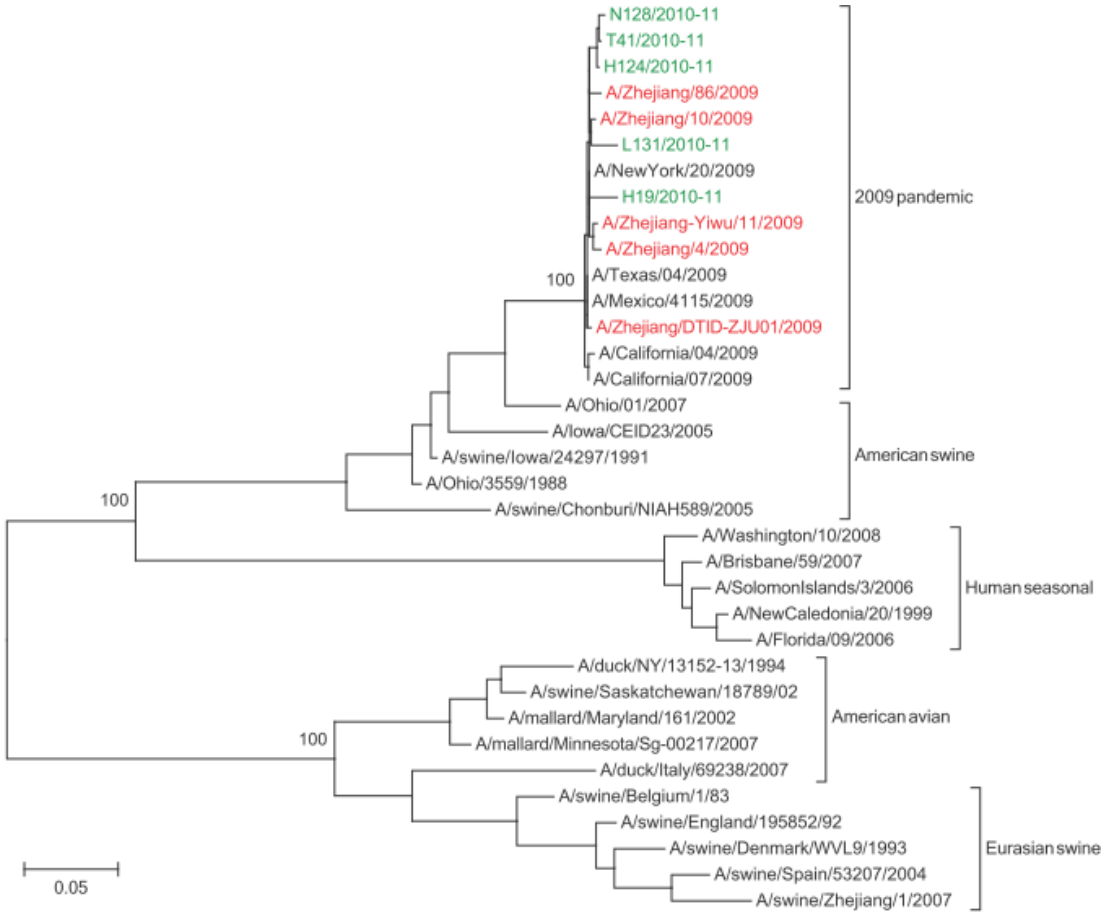

Figure 1. Maximum likelihood phylogenic tree for representative HA1 nucleotide sequences. The 2009 Zhejiang viruses are colored in red and 2010-2011 Zhejiang viruses are colored in green. The numbers near the nodes indicate bootstrap values.

Effects of polymorphisms

According to the ISM concept (see methods), mutations in HA1 which alter the amplitude of the dominant peak at F(0.086) would potentially influence the binding affinity of the 2009 pandemic viruses. We inspected the IS for the 2009-2011 Zhejiang viruses individually, and compared their amplitudes at F(0.086) with that of the consensus HA1 sequence (Figure 3A). Both sequences that can highly increase and decrease the amplitude were found (Figure 3B). To further identify the underlying mutations that contribute most changes, we calculated the variation amount for each single amino acid mutation, taking the consensus HA1 sequence as the control (Figure 3B).

The most common mutation in the 2009 Zhejiang viruses is S128P, which remarkably increases the amplitude at F(0.086) (7.7%). Two successive mutations that increase the amplitude, A73S (5.5%) and D222G (3.7%), may play important roles in the emergence of the lethal strain A/Zhejiang-Yiwu/11/2009. During 2010-2011, more muta-tions that can increase and decrease the amplitude occurred, and many of them were in one sequence such as H19 and L131. However, the peak frequency remains the same.

Polymorphic sites in 3D structure

We mapped the positions of the critical polymorphic sites to the 3D structure of HA1 of the 2009 pandemic virus (see methods). Most of the sites are located in disordered regions which are easily exposed on the protein surface (Figure 4). In general, the receptor binding site (RBS) of HA is at the membrane distal end, which is composed of three elements: 190-helix (residues 184-191), 220-loop (residues 218-225) and 130-loop (residues 131-135). In our result, four polymorphic sites, K219I, D222G, G225R and A134T are located in the RBS domain (Figure 4). It is of note that the mutation D222G is found in the lethal strain A/Zhejiang-Yiwu/11/2009. Two mutations, K219I and A134T, which have reverse effects on the amplitude at F(0.086), together occurred in the 2010-2011 strain H19 (Figure 3B). The most common polymorphic sites, S128P, are also located quite closely to the RBS domain.

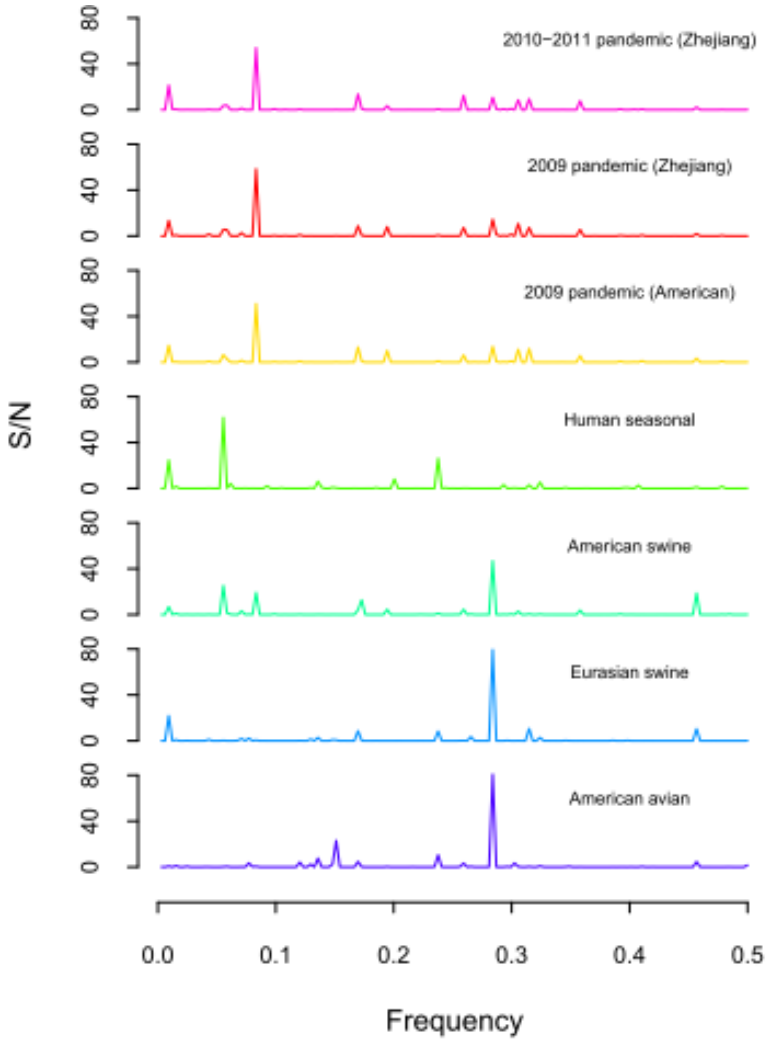

Figure 2. CIS of HA1 sequences from Figure 1. Each H1N1 subtype group contains five HA1 sequences. The peak frequency of American swine, Eurasian swine and American avian viruses is F(0.285). The peak frequency of human seasonal viruses is F(0.058). And the peak frequency of 2009 pandemic viruses is F(0.086).

DISCUSSION

The HA1 subunit is important for the receptor recognition and host infection of influenza viruses. The phylogenic tree of HA1 showed that the recent H1N1 viruses circulating in Zhejiang were all derived from the 2009 pandemic viruses in North American (Figure 1). Although the viruses experienced local transmission since imported, the CIS of HA1 showed that their biochemical properties and receptor preferences have not undergo significant switches (Figure 2). It may be because the population here is not great enough for the occurence of the preference receptors mutation.

Nonetheless, a lot of polymorphisms in HA1 during local transmission may still modify their receptor binding affinity (Figure 3). It was indicated that the mutation of the preference receptors may experience a long period accumulation of none sense mutations during the transmission of the influenza virus. For example, the most common polymorphism, S128P, whose position is close to the RBS domain (Figure 4), can greatly increase the dominant peak in IS. The mutation happened in the RBS domain, D222G, together with A73S, are critical for the emergence of the lethal strain A/Zhejiang-Yiwu/11/2009 (Figures 3 and 4). In the viruses collected in 2010-2011, more mutations occurred and some of them, such as K219I and A134T, are located in the RBS domain (Figures 3 and 4). These mutations could increase or decrease the amplitude of the dominant peak in IS, but the peak frequency has not been shifted. This result may explain why there were much less infected cases during 2010-2011.

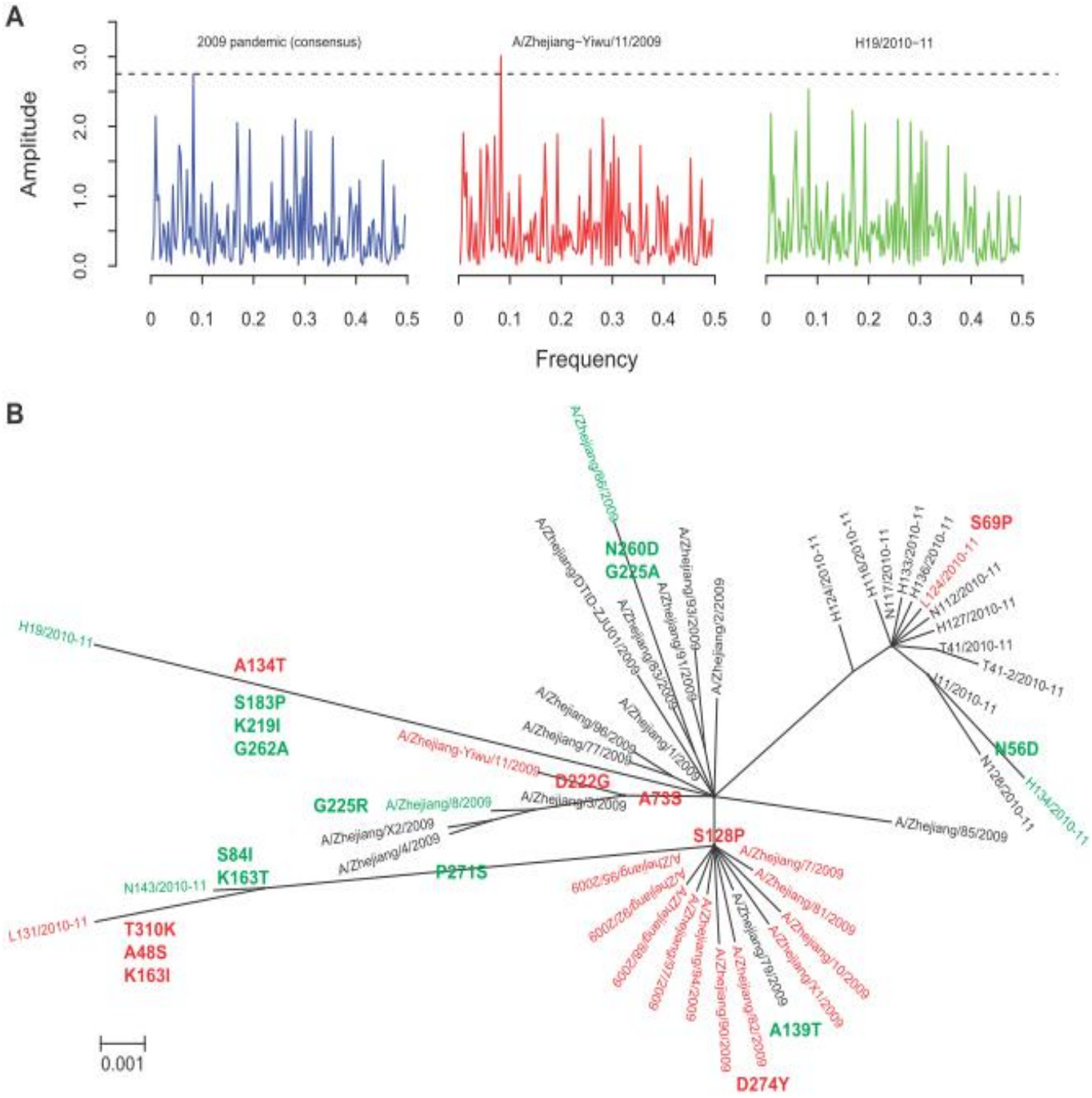

Figure 3. (A) IS of HA1 sequences that can increase or decrease the amplitude at F(0.285). (B) Maximum likelihood phylogenic tree for HA1 of Zhejiang viruses. The sequences that can significantly increase and decrease the amplitude at F(0.086) (> 5%) are colored in red and green, respectively (Supplementary Table 1 for full results). Individual mutations that can significantly increase and decrease the amplitude (>3%) are marked on the branches in red and green, respectively (Supplementary Table 2 for full results).

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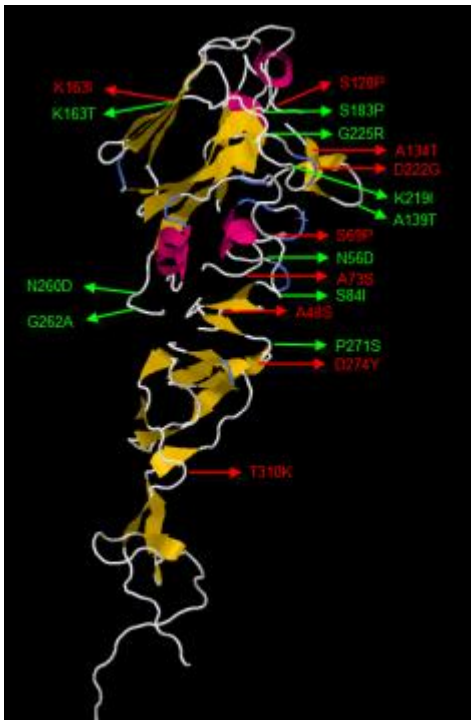

Figure 4. Positions of critical mutations in the 3D structure of HA1. Four polymorphic sites, K219I, D222G, G225R and A134T are located in the receptor binding site (RBS) domain.

(2012ZX10004-210).

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>H19

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GTGCTCTAATGGGTCTCTACAGTGTAGAATATGTATTTAACATTAGG

Supplementary Figure 1. HA sequences of Zhejiang viruses in 2010-2011.

>H116

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Supplementary Figure 1. Contd.

>H124

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Supplementary Figure 1. Contd.

>H127

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Supplementary Figure 1. Contd.

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Supplementary Figure 1. Contd.

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Supplementary Figure 1. Contd.

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Supplementary Figure 1. Contd.

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Supplementary Figure 1. Contd.

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Supplementary Figure 1. Contd.

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Supplementary Figure 1. Contd.

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Supplementary Figure 1. Contd.

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Supplementary Figure 1. Contd.

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Supplementary Figure 1. Contd.

>N112

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Supplementary Figure 1. Contd.

>N117

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Supplementary Figure 1. Contd.

>N119

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Supplementary Figure 1. Contd.

>N128

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Supplementary Figure 1. Contd.

>N143

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Supplementary Figure 1. Contd.

>T41

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Supplementary Figure 1. Contd.

>T41-2.seq

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Supplementary Figure 1. Contd.

Supplementary Table 1. Amplitude of HA1 sequences at the frequency F(0.086) in IS

Sequence	Amplitude	∆Amplitude (%)
L131	3.199591113	0.162405584
AEW25555|A/Zhejiang/82/2009	3.186876596	0.157786423
ACX83577|A/Zhejiang-Yiwu/11/2009	3.009516236	0.093351729
AEW25306|A/Zhejiang/10/2009	2.955433177	0.073703453
AEW25446|A/Zhejiang/7/2009	2.955433177	0.073703453
AEW25545|A/Zhejiang/81/2009	2.955433177	0.073703453
AEW25610|A/Zhejiang/88/2009	2.955433177	0.073703453
AEW25646|A/Zhejiang/92/2009	2.955433177	0.073703453
AEW25669|A/Zhejiang/95/2009	2.955433177	0.073703453
AEW25629|A/Zhejiang/90/2009	2.952695007	0.072708681
AEW25662|A/Zhejiang/94/2009	2.943531543	0.069379611
AEW25297|A/Zhejiang/X1/2009	2.931615066	0.065050377
L124	2.920108881	0.060870201
AEW25687|A/Zhejiang/97/2009	2.90099372	0.053925698
AEW25331|A/Zhejiang/X2/2009	2.890911976	0.050263019
AEW25349|A/Zhejiang/3/2009	2.87850834	0.045756801
AEW25367|A/Zhejiang/4/2009	2.85351423	0.036676486
H127	2.823128586	0.025637438
AEW25654|A/Zhejiang/93/2009	2.81716857	0.023472175
H124	2.79290967	0.014658961
AEW25678|A/Zhejiang/96/2009	2.79242219	0.014481861
N112	2.78569794	0.012038953
H116	2.781410307	0.010481264
H133	2.781410307	0.010481264
H136	2.781410307	0.010481264
N117	2.781410307	0.010481264
T41	2.781410307	0.010481264
AEW25519|A/Zhejiang/79/2009	2.780827576	0.010269559
consensus|2009/pandemic	2.752559063	-3.41E-07
ACR54964|A/Zhejiang/1/2009	2.744906882	-0.002780364
AEW25564|A/Zhejiang/83/2009	2.744906882	-0.002780364
AEW25582|A/Zhejiang/85/2009	2.744906882	-0.002780364
AEW25637|A/Zhejiang/91/2009	2.744906882	-0.002780364
ACS68822|A/Zhejiang/2/2009	2.744295317	-0.003002544
AEW25501|A/Zhejiang/77/2009	2.739547065	-0.004727575
J11	2.723234449	-0.010653919
T41-2	2.723234449	-0.010653919
N128	2.710786104	-0.01517638
ACT21941|A/Zhejiang/DTID-ZJU01/2009	2.708636777	-0.015957226
AEW25528|A/Zhejiang/8/2009	2.589668736	-0.059178097
H19	2.531133011	-0.080444019
N143	2.426568687	-0.118432046
H134	2.365201369	-0.14072668
AEW25590|A/Zhejiang/86/2009	2.291612214	-0.167461485

Supplementary Table 2. Amplitude at the frequency F(0.086) for each polymorphic site

Sequence	Site	Reference	Mutation	Amplitude	∆Amplitude (%)
AEW25555|A/Zhejiang/82/2009	274	D	Y	2.976219379	0.08125541
AEW25306|A/Zhejiang/10/2009	128	S	P	2.963583639	0.076664868
AEW25446|A/Zhejiang/7/2009	128	S	P	2.963583639	0.076664868
AEW25519|A/Zhejiang/79/2009	128	S	P	2.963583639	0.076664868
AEW25545|A/Zhejiang/81/2009	128	S	P	2.963583639	0.076664868
AEW25555|A/Zhejiang/82/2009	128	S	P	2.963583639	0.076664868
AEW25610|A/Zhejiang/88/2009	128	S	P	2.963583639	0.076664868
AEW25629|A/Zhejiang/90/2009	128	S	P	2.963583639	0.076664868
AEW25646|A/Zhejiang/92/2009	128	S	P	2.963583639	0.076664868
AEW25662|A/Zhejiang/94/2009	128	S	P	2.963583639	0.076664868
AEW25669|A/Zhejiang/95/2009	128	S	P	2.963583639	0.076664868
AEW25687|A/Zhejiang/97/2009	128	S	P	2.963583639	0.076664868
AEW25297|A/Zhejiang/X1/2009	128	S	P	2.963583639	0.076664868
L131	128	S	P	2.963583639	0.076664868
N143	128	S	P	2.963583639	0.076664868
H19	134	A	T	2.942887997	0.069146176
L131	310	T	K	2.935200949	0.066353485
ACX83577|A/Zhejiang-Yiwu/11/2009	73	A	S	2.905032985	0.055393515
AEW25349|A/Zhejiang/3/2009	73	A	S	2.905032985	0.055393515
AEW25367|A/Zhejiang/4/2009	73	A	S	2.905032985	0.055393515
AEW25528|A/Zhejiang/8/2009	73	A	S	2.905032985	0.055393515
AEW25331|A/Zhejiang/X2/2009	73	A	S	2.905032985	0.055393515
L131	48	A	S	2.886434898	0.048636862
L124	69	S	P	2.877230499	0.04529292
L131	163	K	I	2.859377492	0.038806953
ACX83577|A/Zhejiang-Yiwu/11/2009	222	D	G	2.855693714	0.037468643
AEW25297|A/Zhejiang/X1/2009	62	L	P	2.811631381	0.021460872
AEW25654|A/Zhejiang/93/2009	290	L	P	2.806086307	0.019446356
H127	283	K	N	2.802238062	0.018048295
AEW25501|A/Zhejiang/77/2009	113	R	K	2.798878436	0.016827749
AEW25678|A/Zhejiang/96/2009	113	R	K	2.798878436	0.016827749
H191	293	Q	R	2.792353486	0.014457246
H116	197	A	T	2.789901467	0.013566431
H124	197	A	T	2.789901467	0.013566431
H127	197	A	T	2.789901467	0.013566431
H133	197	A	T	2.789901467	0.013566431
H134	197	A	T	2.789901467	0.013566431
H136	197	A	T	2.789901467	0.013566431
J11	197	A	T	2.789901467	0.013566431
L124	197	A	T	2.789901467	0.013566431
N112	197	A	T	2.789901467	0.013566431
N117	197	A	T	2.789901467	0.013566431
N128	197	A	T	2.789901467	0.013566431
T41	197	A	T	2.789901467	0.013566431
T41-2	197	A	T	2.789901467	0.013566431
H124	19	V	I	2.771294325	0.006806489

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AEW25654|A/Zhejiang/93/2009	321	V	I	2.770897921	0.006662476
H19	250	V	I	2.768087662	0.005641514
AEW25331|A/Zhejiang/X2/2009	296	H	P	2.764133887	0.004205114
H116	185	S	T	2.757294768	0.001720474
H127	185	S	T	2.757294768	0.001720474
H133	185	S	T	2.757294768	0.001720474
H134	185	S	T	2.757294768	0.001720474
H136	185	S	T	2.757294768	0.001720474
J11	185	S	T	2.757294768	0.001720474
L124	185	S	T	2.757294768	0.001720474
N112	185	S	T	2.757294768	0.001720474
N117	185	S	T	2.757294768	0.001720474
N128	185	S	T	2.757294768	0.001720474
T41	185	S	T	2.757294768	0.001720474
T41-2	185	S	T	2.757294768	0.001720474
H19	234	V	I	2.755676606	0.001132598
AEW25564|A/Zhejiang/83/2009	286	I	L	2.752559063	0
AEW25582|A/Zhejiang/85/2009	267	I	L	2.752559063	0
ACT21941|A/Zhejiang/DTID-ZJU01/2009	32	L	I	2.752559063	0
ACS68822|A/Zhejiang/2/2009	100	E	G	2.751929585	-0.000228688
AEW25629|A/Zhejiang/90/2009	140	G	E	2.749916344	-0.000960095
N112	258	E	K	2.748497604	-0.001475521
L131	295	I	V	2.74532357	-0.002628642
N143	295	I	V	2.74532357	-0.002628642
ACX83577|A/Zhejiang-Yiwu/11/2009	203	S	T	2.744906882	-0.002780024
ACR54964|A/Zhejiang/1/2009	203	S	T	2.744906882	-0.002780024
AEW25306|A/Zhejiang/10/2009	203	S	T	2.744906882	-0.002780024
ACS68822|A/Zhejiang/2/2009	203	S	T	2.744906882	-0.002780024
AEW25349|A/Zhejiang/3/2009	203	S	T	2.744906882	-0.002780024
AEW25367|A/Zhejiang/4/2009	203	S	T	2.744906882	-0.002780024
AEW25446|A/Zhejiang/7/2009	203	S	T	2.744906882	-0.002780024
AEW25501|A/Zhejiang/77/2009	203	S	T	2.744906882	-0.002780024
AEW25519|A/Zhejiang/79/2009	203	S	T	2.744906882	-0.002780024
AEW25528|A/Zhejiang/8/2009	203	S	T	2.744906882	-0.002780024
AEW25545|A/Zhejiang/81/2009	203	S	T	2.744906882	-0.002780024
AEW25555|A/Zhejiang/82/2009	203	S	T	2.744906882	-0.002780024
AEW25564|A/Zhejiang/83/2009	203	S	T	2.744906882	-0.002780024
AEW25582|A/Zhejiang/85/2009	203	S	T	2.744906882	-0.002780024
AEW25590|A/Zhejiang/86/2009	203	S	T	2.744906882	-0.002780024
AEW25610|A/Zhejiang/88/2009	203	S	T	2.744906882	-0.002780024
AEW25629|A/Zhejiang/90/2009	203	S	T	2.744906882	-0.002780024
AEW25637|A/Zhejiang/91/200	203	S	T	2.744906882	-0.002780024
AEW25646|A/Zhejiang/92/2009	203	S	T	2.744906882	-0.002780024
AEW25654|A/Zhejiang/93/2009	203	S	T	2.744906882	-0.002780024
AEW25662|A/Zhejiang/94/2009	203	S	T	2.744906882	-0.002780024
AEW25669|A/Zhejiang/95/2009	203	S	T	2.744906882	-0.002780024
AEW25678|A/Zhejiang/96/2009	203	S	T	2.744906882	-0.002780024

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AEW25687|A/Zhejiang/97/2009	203	S	T	2.744906882	-0.002780024
AEW25297|A/Zhejiang/X1/2009	203	S	T	2.744906882	-0.002780024
AEW25331|A/Zhejiang/X2/2009	203	S	T	2.744906882	-0.002780024
H19	203	S	T	2.744906882	-0.002780024
H116	203	S	T	2.744906882	-0.002780024
H124	203	S	T	2.744906882	-0.002780024
H127	203	S	T	2.744906882	-0.002780024
H133	203	S	T	2.744906882	-0.002780024
H134	203	S	T	2.744906882	-0.002780024
H136	203	S	T	2.744906882	-0.002780024
J11	203	S	T	2.744906882	-0.002780024
L124	203	S	T	2.744906882	-0.002780024
L131	203	S	T	2.744906882	-0.002780024
N112	203	S	T	2.744906882	-0.002780024
N117	203	S	T	2.744906882	-0.002780024
N128	203	S	T	2.744906882	-0.002780024
N143	203	S	T	2.744906882	-0.002780024
T41	203	S	T	2.744906882	-0.002780024
T41-2	203	S	T	2.744906882	-0.002780024
AEW25662|A/Zhejiang/94/2009	132	V	I	2.741087914	-0.004167449
H116	143	S	G	2.738645943	-0.005054612
H124	143	S	G	2.738645943	-0.005054612
H127	143	S	G	2.738645943	-0.005054612
H133	143	S	G	2.738645943	-0.005054612
H134	143	S	G	2.738645943	-0.005054612
H136	143	S	G	2.738645943	-0.005054612
J11	143	S	G	2.738645943	-0.005054612
L124	143	S	G	2.738645943	-0.005054612
N112	143	S	G	2.738645943	-0.005054612
N117	143	S	G	2.738645943	-0.005054612
N128	143	S	G	2.738645943	-0.005054612
T41	143	S	G	2.738645943	-0.005054612
T41-2	143	S	G	2.738645943	-0.005054612
H19	252	R	I	2.737157302	-0.005595433
AEW25590|A/Zhejiang/86/2009	28	H	Q	2.736997758	-0.005653395
ACX83577|A/Zhejiang-Yiwu/11/2009	70	L	F	2.731560163	-0.007628864
AEW25349|A/Zhejiang/3/2009	70	L	F	2.731560163	-0.007628864
AEW25367|A/Zhejiang/4/2009	70	L	F	2.731560163	-0.007628864
AEW25528|A/Zhejiang/8/2009	70	L	F	2.731560163	-0.007628864
AEW25331|A/Zhejiang/X2/2009	70	L	F	2.731560163	-0.007628864
AEW25367|A/Zhejiang/4/2009	190	S	R	2.725873831	-0.009694699
H19	255	F	C	2.713950333	-0.014026485
ACT21941|A/Zhejiang/DTID-ZJU01/2009	223	Q	R	2.708636777	-0.015956891
AEW25501|A/Zhejiang/77/2009	150	W	C	2.703241088	-0.017917136
N128	125	N	D	2.701204521	-0.018657017
AEW25687|A/Zhejiang/97/2009	138	H	Y	2.700114317	-0.019053087
H134	235	E	K	2.688020143	-0.023446879

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J11	235	E	K	2.688020143	-0.023446879
N128	235	E	K	2.688020143	-0.023446879
T41-2	235	E	K	2.688020143	-0.023446879
L131	199	V	A	2.674398408	-0.028395632
N143	199	V	A	2.674398408	-0.028395632
AEW25297|A/Zhejiang/X1/2009	283	K	R	2.670788537	-0.029707092
H19	262	G	A	2.662396684	-0.032755838
L131	271	P	S	2.654381096	-0.035667887
N143	271	P	S	2.654381096	-0.035667887
AEW25590|A/Zhejiang/86/2009	225	G	A	2.648715288	-0.037726266
H19	219	K	I	2.634240905	-0.042984784
N143	163	K	T	2.593808194	-0.057673919
AEW25519|A/Zhejiang/79/2009	139	A	T	2.584236204	-0.061151407
H19	183	S	P	2.564419891	-0.068350639
N143	84	S	I	2.546651529	-0.074805855
AEW25528|A/Zhejiang/8/2009	225	G	R	2.465644343	-0.104235627
H134	56	N	D	2.409402254	-0.124668282
AEW25590|A/Zhejiang/86/2009	260	N	D	2.407361827	-0.125409565