Origin and Molecular Characteristics of a Novel 2013 Avian Influenza A(H6N1) Virus Causing Human Infection in Taiwan

To the Editor—On 20 May 2013, the world’s first human-infected case of H6N1 bird flu was reported in Taiwan. A novel avian-origin influenza A(H6N1) virus was confirmed by the National Influenza Center, Centers for Disease Control, Taiwan, and the patient has already recovered. The H6 subtype influenza viruses were first identified in turkeys in 1965, and make up one of the most commonly recognized subtypes in domestic ducks in southern China [1]. Previous studies indicated that the H6N1 virus is low pathogenic [2]. In this study, we investigated the molecular characteristics of the novel avian influenza A(H6N1) virus and performed phylogenetic and coalescent analyses to infer the potential origins.

We first conducted a sequence identical analysis using nucleotide BLAST for all 8 segments of the novel H6N1 virus across 2 Avian influenza virus sequence databases (GISAID, NCBI). The PB1 gene of the novel human influenza A/Taiwan/2/2013(H6N1) (EPI_ISL_143275) has the highest nucleotide sequence similarity to A/chicken/Taiwan/PF3/02(H6N1) at 95.8%, whereas the remaining 7 genes showed that the highest nucleotide sequence similarity to A/chicken/Taiwan/A2837/2013 (H6N1) ranged from 96.2% (NA) to 99.5% (NP). We also constructed the maximum likelihood phylogenetic trees for each genome segment using the program PhyML3.0 [3]. The results of phylogenetic analyses showed that all 8 genes of this virus were clustered in the Taiwan lineage. Taking sampling collection schedules into consideration, the closest relative of A/Taiwan/2/2013(H6N1) is A/chicken/Taiwan/A2837/2013, suggesting the latter might be the precursor of the novel virus. Our results indicated A/Taiwan/2/2013 (H6N1) was reassorted from A/chicken/Taiwan/0101/2012(H5N2) (PB2 and PA genes), A/chicken/Taiwan/A1997/2012

Figure 1. Schematic diagram of origins of the novel reassortant human influenza A(H6N1) virus. The colors of the gene segments in the ovals indicate their origin. Dotted lines represent the different times when the most closely related sequences (identified from phylogenetic analyses) of the novel H6N1 virus were collected.
(H5N2) (M gene), A/chicken/Taiwan/ch1006/04(H6N1) (HA gene), and A/chicken/Taiwan/TC135/2010(H6N1) (PB1, NP, NA, and NS genes) (Figure 1).

Furthermore, we investigated the molecular signatures of the novel H6N1 virus. One hundred HA and NA gene sequences with higher similarity were chosen for amino acid alignment analysis. For HA, the strain A/Taiwan/2/2013 had a low pathogenicity because its HA1/HA2 connecting peptide region (QIAATR/GIF) lacked the multibasic amino acids, which is the signature of highly pathogenic H5 and H7 influenza viruses [4, 5]. In contrast, the sequence before the cleavage site in most H6N1 influenza viruses is QIETR or QIKTR. Most of the mutation sites were in the HA1 part, whereas only 2 changes were found in the HA2 part. Interestingly, in comparison with chicken A/H6N1 viruses, we found 2 unusual mutation sites in the novel human A/H6N1: P200Land A301 T (H6 numbering), which located closely to the domain of HA receptor binding. Moreover, at the critical HA receptor binding site (239–244) (H6 numbering) of this novel H6N1, the position 228 in HA was S, as in human-adapted H3 strains, which effectively raises the possibility that H6N1 might transmit to humans [6]. For NA, the novel virus showed a 12-amino acid deletion in the NA stalk and 5 mutation sites: S31L, G189N, K265R, V389M, and D451E (H6 numbering). The length variation of the NA stalk may affect the host range of influenza A virus [7, 8]. Our results on the origin and molecular characteristics of the novel H6N1 may be useful for future influenza surveillance.

Notes

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