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Molecular Epidemiology of a Post-Influenza Pandemic Outbreak of Acute Respiratory Infections in Korea Caused by Human Adenovirus Type 3

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An outbreak of upper respiratory tract infections associated with human adenovirus (HAdV) occurred on a national scale in Korea from September to December 2010, following a major H1N1 influenza pandemic. Data from the Korea Influenza and Respiratory Surveillance System (KINRESS) showed an unusually high positive rate accounting for up to 20% of all diagnosed cases. To determine the principal cause of the outbreak, direct polymerase chain reaction (PCR) amplification followed by sequence analysis targeting parts of the *hexon* gene of HAdV was performed. Serotypes of 1,007 PCR-diagnosed HAdV-positive samples from patients with an acute upper respiratory tract illness were determined and epidemiological characteristics including major aged group and clinical symptoms were analyzed. The principal symptom of HAdV infections was fever and the vulnerable aged group was 1–5 years old. Based on sequence analysis, HAdV-3 was the predominant serotype in the outbreak, with an incidence of 74.3%. From the beginning of 2010 until May, the major serotypes were HAdV-1, 2, and 5 (70–100%) in any given period. However, an outbreak dominated by HAdV-3 started between July and August and peaked in September. Phylogenetic analysis revealed that there was no genetic variation in HAdV-3. The results demonstrated that an outbreak of upper respiratory illness followed by H1N1 influenza pandemic in Korea was caused mainly by emerged HAdV-3. ***J. Med. Virol. 87:10–17, 2015.***

KEY WORDS: human adenovirus; molecular epidemiology; post-pandemic outbreak

INTRODUCTION

Human adenoviruses (HAdVs) in the Family *Adenoviridae*, genus *Mastadenovirus* are responsible for various illnesses, including respiratory tract infections, conjunctivitis, cystitis, and gastroenteritis [Kunz and Ottolini, 2010]. Typically, HAdV-B species (types 3, 7, 12, 14, and 55), HAdV-C (types 1, 2, 5, and 6), and HAdV-E (type 4) are closely associated with respiratory tract infections [Metzger et al., 2007; Kajon et al., 2010; Walsh et al., 2010; Tang et al., 2013]. Identification of serotypes is important because the pathogenesis of HAdV infection is determined mainly by serotypes. Based on nucleotide and amino acid sequences of the hypervariable region in the *hexon* gene, phylogenetic analysis has been used for the clustering and typing of HAdVs [Crawford-Miksza and Schnurr, 1996a; Biere and Schweiger, 2010]. Accordingly, phylogenetic analysis can facilitate molecular epidemiological investigations of HAdV outbreaks.

Respiratory HAdV infections have been closely associated with acute respiratory infections such as febrile illness, pharyngitis, and coryza (common cold). Repeated outbreaks of such diseases have been reported worldwide [Ryan et al., 2002; Kim et al., 2003; Chang et al., 2008]. In the same context, respiratory HAdV infections can be identified from patients with an upper respiratory tract infection

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throughout the entire year, with an average detection rate of 4% in Korea [Lee et al., 2010]. However, in 2010—after a major H1N1 influenza pandemic in 2009—an outbreak of HAdV infections occurred in Korea. This study aimed to identify the major type of HAdV involved through direct PCR amplification followed by *hexon* gene sequence analysis. The public health impact based on clinical features of the outbreak is also emphasized. This is believed to be the first report of a nationwide outbreak of respiratory adenovirus infections in Korea.

MATERIALS AND METHODS

Specimen Collection and Study Object

In 2010, 13,502 throat swabs from patients with an acute respiratory infections exhibiting a fever (>38°C), coughing, sore throat, and runny nose were collected and used to detect viral causative agents through the Korea Influenza and Respiratory Viruses Surveillance system (KINRESS), which obtains routinely clinical specimens from outpatients with acute respiratory infections who seek primary clinical care from about 100 hospitals nationwide in Korea. Specimens were placed in virus transport medium (BD, Sparks, MD) and sent to 17 local institutes of health and environmental research maintained at 4°C to be tested for major respiratory viruses including HAdVs. The remained samples were stored at −70°C until use. Because an abnormally high positive rate of HAdV was observed nationwide from July 2010 until the end of the year, all positive cases (n = 1,007) of HAdVs were selected and then subjected to differentiate serotypes retrospectively. To compare any difference in HAdV prevalence between the pre- and post-pandemic phases, 91 samples of nasal aspirates taken in 2008 before the H1N1 influenza pandemic were collected through the acute respiratory infection network. The study was approved by the Ethics Committee of the Korean National Institute of Health (Approval # 2008; 2012-09CON-03-4C, 2010; 2010-03EXP-1-R).

Statistical Analysis of Clinical Symptoms

Characteristics of the clinical symptoms associated with HAdV infections as well as records of all enrolled patients with acute respiratory infections were analyzed from the clinical records compiled via acute respiratory infections network for 2008 and KINRESS for 2010. Logistic regression analysis with odds ratio values were performed to test the relationships between HAdV infection and clinical symptoms using SAS software (version 9.2; SAS Institute, Cary, NC).

Direct PCR Amplification and Genome Sequencing

Total viral DNA was extracted from 140 μl aliquots of specimens using Quickgene-810 (Fujifilm, Tokyo, Japan) following the manufacturer's protocol. To amplify part of the *hexon* gene, primer pairs AV3R (5′-ATGTGGAAICAGGCIGTIGACAG-3′) and AV5L (5′-CGGTGGTGITTIAAIGGITTIACITTGTCCAT-3′) [Crafford-Miksza et al., 1999] were used to produce a 458 base pair (bp) fragment (position 19,552–20,009; accession # DQ086466). The PCR was performed using SP-*Taq* polymerase (Cosmogenetech, Seoul, Korea) to maximize fidelity of DNA amplification. The amplification products were analyzed by electrophoresis in 2% agarose gels (Gendepot, Barker, TX) and they were visualized using SYBR safe DNA gel stain (Invitrogen, Carlsbad, CA) under ultraviolet light. The PCR products were then purified using a QIAquick Spin column purification system (Qiagen, Hilden, Germany) to remove any trace of primers and analyzed directly on an ABI3730 sequencer (Applied Biosystems, Foster City, CA).

Identification of HAdV Type and Phylogenetic Analysis

Partial *hexon* gene sequences were analyzed using DNASTAR 8.0 (Lasergene, Madison, WI) and aligned against other available HAdV sequences using ClustalW. To type HAdV, the nucleotide sequence homology was inferred from the identity scores obtained using the BLASTn program (National Center for Biotechnology Information, Bethesda, MD). MEGA4 was used to create phylogenetic trees through the neighbor-joining method based on the Kimura 2-parameter distance matrix listed in the software, and bootstrap values were obtained from a random sampling of 1,000 replicates [Tamura et al., 2007]. Reference HAdV sequences were obtained from GenBank (http://www.ncbi.nlm.nih.gov/genbank/) and used for phylogenetic analysis.

Nucleotide Sequence Accession Numbers

The nucleotide sequences of the partial *hexon* genes for strains identified in this study have been deposited in the GenBank nucleotide sequence database under serial accession numbers from KC747631 to KC747649. Reference sequences with accession number used in this study were given in supplementary Table SI.

RESULTS

Prevalence of HAdVs

From the beginning of 2010 to the end of the year, an outbreak of respiratory infections associated with HAdV in Korea was examined retrospectively because of the significantly high positive rate of HAdV found in samples. The monthly positive rates of HAdV from throat swabs at the 17 local institutes of health and environmental research units during the period are shown in Figure 1 and compared with those taken in 2008 as a baseline.

The median positive rate of HAdV in patients with an acute respiratory infection in the baseline period

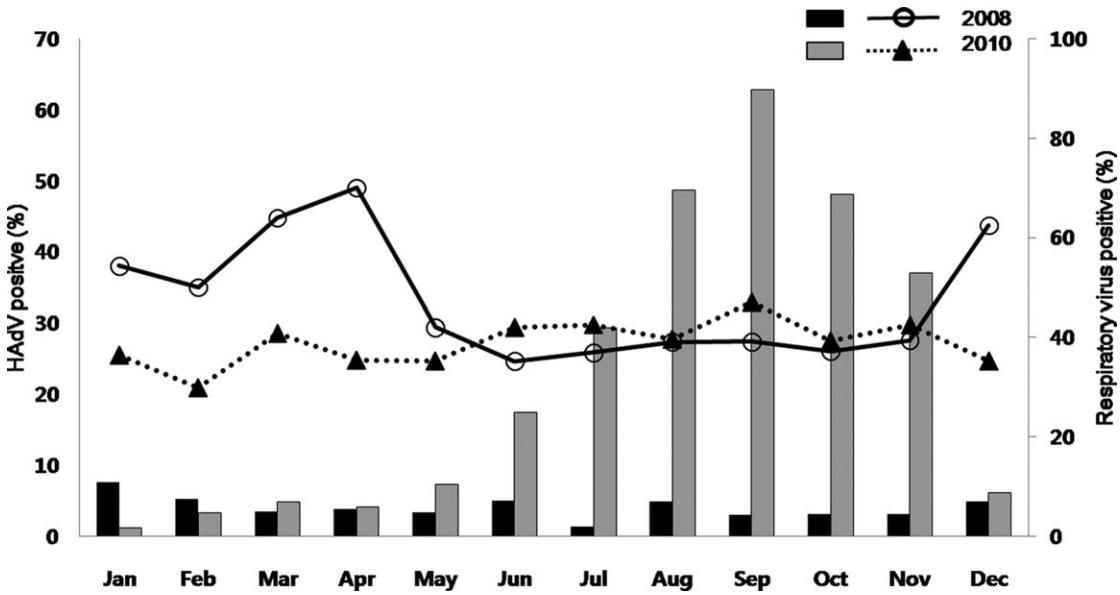

Fig. 1. Monthly positive rates of HAdV infections in 2008 and 2010. The 2-year distribution of HAdV-positive rates (left y-axis; bars) out of the total incidence of respiratory viruses (right y-axis; lines) was significantly different ($P = 0.009$). In 2010, number of specimens were maintained certain level over the year, however the positive rate of HAdV was drastically increased from Jun to Nov.

(previous 3-year average) was 2.0% (range 1.0–5.0%); however, during the outbreak period from June to December 2010, the rate increased significantly to 16.7% (range 3.8–31.3%; $P < 0.001$; Fig. 2). The majority of these HAdV positive cases (up to 77.9%) were identified from children (1–5 years old aged group; Fig. 3) and the highest positive rate was observed at 2 years old aged group (24.2% in 1–5 years old aged group) in 2010. No gender bias was identified in a given aged group. Human respiratory syncytial viruses (hRSVs), human rhinoviruses (hRVs), human metapneumovirus (hMPV), human para-influenzaviruses (hPIVs), human coronaviruses (hCoVs), human bocaviruses (hBoVs), and influenza viruses were also detected through the KINRESS databank. Of these, hRVs was the leading co-infecting agent among the cases of HAdV infection with a positive rate of 25.3% in 2008 and 6.6% in 2010. Other respiratory viruses were also identified as co- or multi-infecting agents with positive rates ranging from 1.1% to 2.2%.

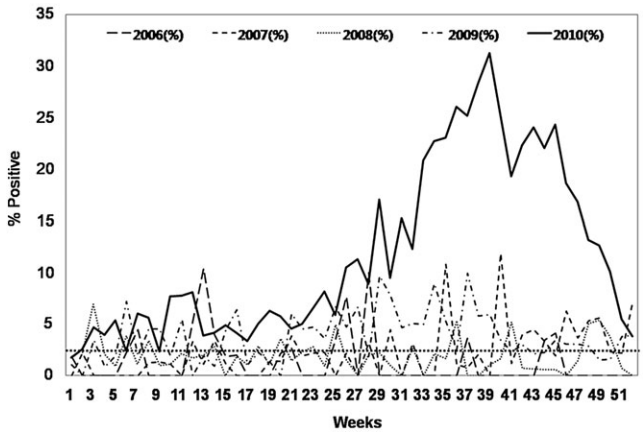

Fig. 2. Positive rates of HAdV infections in five consecutive years. The median positive rate of adenoviruses detected in the baseline periods (previous 3-year average) was 2.0% (straight dotted line; range 1.0–5.0%). However, during the outbreak period, from June to December 2010, the positive rate increased significantly to 16.7%.

Identification of HAdV

The serotype of each adenovirus was determined by sequencing analysis followed by direct PCR of a part of the *hexon* gene. From the beginning of 2010 until May, the major serotypes were types 1, 2, and 5 (70–100%) in any given period. However, an outbreak dominated by type 3 started between July and August and peaked in September. Based on the sequence analysis, HAdV-3 was the predominant serotype, in this phase of the outbreak, at 74.3%. Besides HAdV-3, 12 more serotypes were also identified: HAdV-2 (10.1%), HAdV-1 (8.0%), HAdV-5 (3.2%), HAdV-4 (2.3%), HAdV-6 (0.8%), HAdV-8 (0.6%), HAdV-7 (0.2%), HAdV-11 (0.1%), HAdV-19 (0.1%), HAdV-34 (0.1%), HAdV-41 (0.1%), and HAdV-55 (0.1%). By contrast, only six serotypes (HAdV-1, HAdV-2, HAdV-3, HAdV-4, HAdV-5, and HAdV-6) were identified in samples from 2008. HAdV-3 was also the major serotype at that time at 40.7%. However, HAdV-2 (25.3%) and HAdV-1 (23.1%) comprised larger

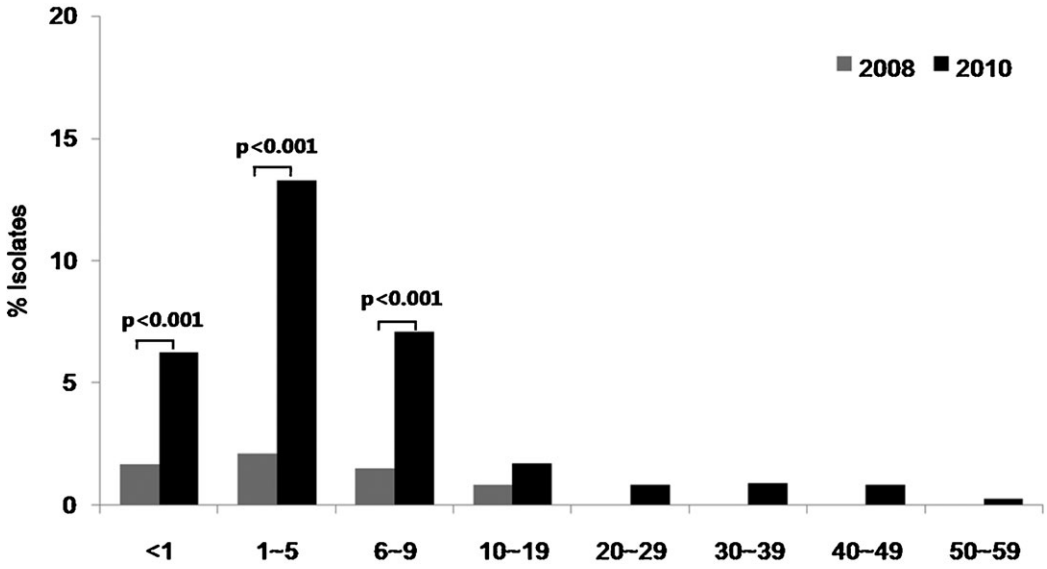

Fig. 3. Age distribution of HAdV-3 positive patients in each age group; 80.9% of patients were aged less than 5 years old.

proportions in 2008 than in 2010 (Fig. 4). Interestingly, HAdV-41, which is known to be a gastroenteritic cause of HAdV infection, was also confirmed from a patient with acute respiratory infections.

Clinical Features of HAdV Infection

The clinical features of overall adenovirus infections are summarized in Table I. Most of the patients had a fever, coughing, runny nose, nasal congestion, and/or sore throat. Over 80% of patients had a febrile illness and approximately half of them had a cough and a runny nose. Symptomatic comparison of patients who were infected with HAdV-3 in the baseline period (2008), there was no significantly elevated proportion of patients with fever and severe infections in the outbreak period (83.8% vs. 89.8%, $P = 0.24$). Instead, coughing, a runny nose, and nasal congestion were significantly lower in 2010 ($P < 0.001$; Fig. 5).

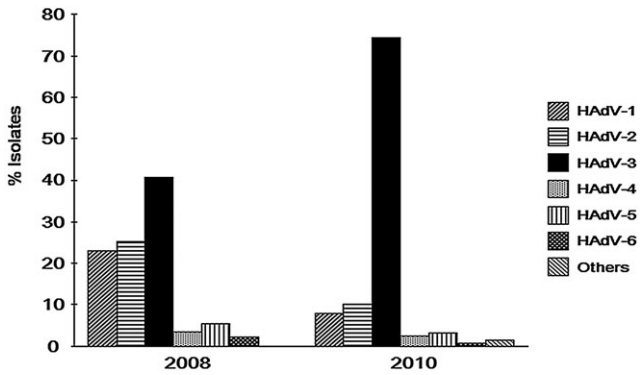

Fig. 4. Serotypes of HAdVs based on the partial *hexon* gene sequence information. HAdV types 1 and 2 were the leading serotype in 2008 whereas HAdV-3 was responsible for one-third of HAdV infections in 2010. Of note, HAdV type 41 was identified in a patient with acute respiratory illness in 2010.

Phylogenetic Analysis

The partial *hexon* gene sequences of 1,007 PCR-positive cases of HAdV from patients with acute respiratory infections were determined. In terms of species A through G, HAdV sequences from the outbreak period did not form a cluster differing from reference sequences. Sequence alignment was also performed to determine the sequence similarities for the leading serotype, HAdV-3. All the HAdV-3 strains isolated in the outbreak period showed high sequence identity (98.15–100%) compared with those in most other years (Fig. 6). One isolate of the gastroenteritis strain HAdV-41 also showed no significant variation from formerly reported sequence information. There were no sequence differences between the HAdVs that were isolated in 2008 and 2010 for all types (HAdV-1, HAdV-2, HAdV-3, HAdV-4, HAdV-5, and HAdV-6).

TABLE I. Major Clinical Symptoms Related with HAdV Infection in 2008 and 2010

Symptoms	2008 Cases (%)	2010 Cases (%)	*P*-value
Fever	70 (76.9)	898 (89.2)	<0.001
Cough	65 (71.4)	463 (46.0)	<0.001
Runny nose	79 (86.8)	488 (48.5)	<0.001
Nasal congestion	51 (56.0)	177 (17.6)	<0.001
Sore throat	11 (12.1)	295 (29.3)	<0.001
Phlegm	23 (25.3)	127 (17.1)	0.05
Chilly	7 (7.7)	150 (14.9)	0.06
Hoarse	4 (4.4)	59 (5.9)	0.565

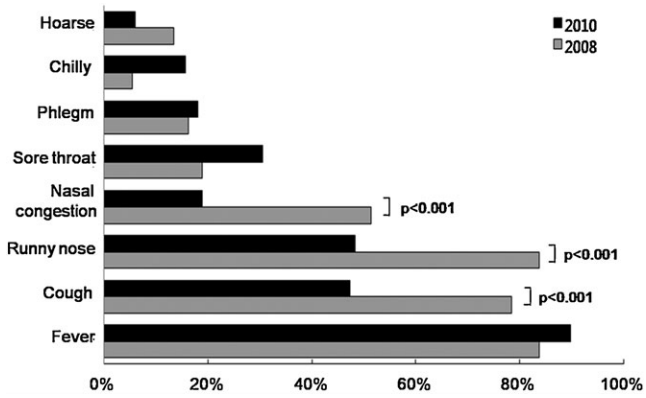

Fig. 5. Clinical symptoms of HAdV-3 infected patients in 2008 and 2010. The leading clinical symptom of HAdV infection was fever. Coughing, runny nose, and nasal congestion were significantly diminished in 2010 ($P < 0.001$).

DISCUSSION

HAdV infection is one of the leading causes of respiratory illness with typical clinical features, seen in community-based surveillance [Cao et al., 2014]. To date, over 57 serotypes of HAdV have been identified, and different serotypes have been correlated with different clinical manifestations [Chu and Pavan-Langston, 1979; Wood, 1988; Gonçalves and de Vries, 2006]. Frequent outbreaks of acute respiratory infections caused by HAdV have been described worldwide. The most frequent serotypes associated with respiratory outbreaks in various countries listed below have been mainly classified into subspecies B (HAdV-11: China, HAdV-7: Korea, HAdV-3: Taiwan), C (HAdV-1 and 2: Malaysia), and E (HAdV-4: USA) [Kajon et al., 2007; Chang et al., 2008; Yang et al., 2009; Abd-Jamil et al., 2010; Lee et al., 2010].

Symptoms caused by HAdV infection range from mild symptoms to severe pneumonia. Furthermore, respiratory illness associated with HAdV can be confused with an influenza-like illness (ILI) including fever, coughing, sore throat, and muscle pain [Tohma et al., 2012]. To avoid the misdiagnosis of HAdV infection from patients with an ILI, a molecular biology technique such as direct PCR is used for discriminating possible causative viral agents. In Korea, the laboratory surveillance system named KINRESS has been targeting outpatients with acute respiratory infections since 2005. Annually, in 1–5% of patients with acute respiratory illness the cause is infection with HAdV and this proportion is consistent with previous reports [Lee et al., 2010a,b].

In the first post-influenza pandemic period, an abrupt outbreak of HAdV was identified starting in June 2010. The median positive rate of adenovirus infections in the baseline period (previous 3-year average) was 2.0%. However, during the HAdV outbreak—from June to December 2010—the mean positive rate increased significantly to 16.7%, ranging from 3.8% to 31.3%.

A total of 1,007 HAdV-positive cases were diagnosed from 13,502 clinical specimens (7.5%) in 2010. Among these, HAdV-3 (74.3% of positive cases) was identified as the major causative agent responsible for this outbreak of respiratory illness. Interestingly, HAdV-41 belonging to subspecies F was isolated from a patient with respiratory illness without diarrhea. Because the HAdV-41 is known to be a causative agent for viral gastroenteritis [Uhnoo et al., 1984] rather than respiratory illness, it remains to be clarified whether this finding solely caused by pathological changes of the virus or not.

Phylogenetic analysis revealed that the outbreak caused by HAdV type 3 during 2010 in Korea seemed not to be related to any specific changes in viral genotypes. Instead, in 2010 this strain played a unique role as a causative agent of respiratory illness. Similar to other reports regarding HAdV infection in patients with respiratory illness, the most affected age group was children aged 1–5 years old (77.9%). Although 1–5 years old aged group took a higher proportion than other aged groups, the positive rate of HAdV-3 in each age group also higher than other aged groups. These result was consistent with previous report that the positive rate of HAdV was the most higher among children less than 5 years of age [Cooper et al., 2000; Chang et al., 2008; Cheng et al., 2008].

To confirm HAdV-3 as the sole causative agent for this outbreak, multiple co-infections by other respiratory viruses together with HAdVs were analyzed. Dual or more multiple infections with hRSVs, hRVs, hMPV, hPIVs, hCoVs, hBoVs, and influenza viruses were studied. The results showed that hRVs were the leading cause of co-infection with HAdV in 2008 (25.3%) and 2010 (6.6%). The incidence of this single infection rate was significantly higher in 2010 (86.4%) than in 2008 (70.3%) ($P < 0.001$). Thus, it is highly feasible that HAdV-3 infection was the sole cause of the outbreak in 2010.

Epidemiological and molecular data presented in this study confirmed that the outbreak in 2010 was not associated with genetic alterations causing a change in the pathology of the major causative agent, HAdV-3, nor with multiple infections with other respiratory viruses.

Because the present study focused on outpatients with acute respiratory infections, severe manifestations such as bronchitis, pneumonia, and bronchiolitis were not scored in this study. Nevertheless, several symptoms associated with HAdV-3 infection such as nasal congestion, runny nose, and coughing were fewer in 2010 when compared with 2008 ($P < 0.001$). Because little is known about the association between disease severity and the virulence-determining factors of HAdV, it is unclear whether these reduced clinical symptoms arose from a particular change in virulence.

In recent years, PCR and sequence analyses targeting the HAdV *hexon* gene encoding a serotype-specific

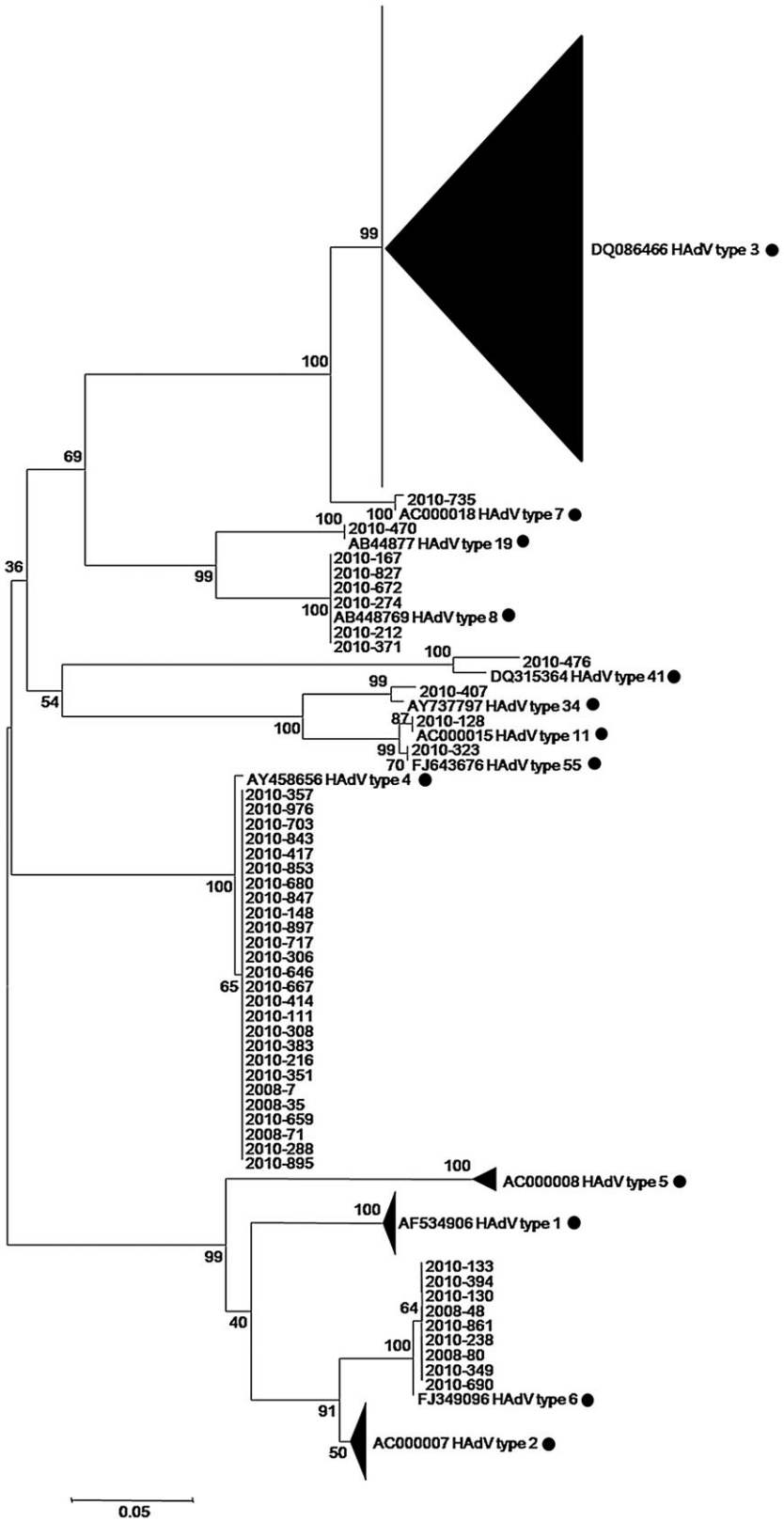

Fig. 6. Phylogenetic analysis of 1,007 HAdV-positive cases based on the partial *hexon* gene sequence information. Mega 4 software was used to generate a phylogenetic tree; 1,000 replicates were performed for bootstrap analysis and values are shown at each branch node. Reference strains for each genotype obtained from GenBank are marked with closed circles (●). Triangular symbols indicate positive cases of HAdVs corresponding with each reference strain.

epitope have enabled rapid identification and classification of the genotypes and serotypes of HAdVs [Craford-Miksza et al., 1999]. The strategy of serotype analysis used in this study was also based on a *hexon* gene sequence and allowed basic molecular biological information on circulating HAdVs to be obtained. Even though HAdVs have DNA as their genetic material, recombination is very frequently reported for this virus, which could be important for HAdV evolution resulting in shifts in its pathology and virulence [Craford-Miksza and Schnurr, 1996b; Walsh et al., 2009; Rebelo-de-Andrade et al., 2010]. One recent report indicated that recombinant HAdVs introduced into the community could produce highly virulent strains with epidemic and lethal potential [Halstead et al., 2010]. Therefore, there might be a limit to explaining the relationship between clinical manifestations and HAdV infections through PCR-based molecular typing targeting just one gene. It would be better to use two or more genomic point comparisons for serotype determination to obtain better evidence for the pathogenicity and disease severity of particular serotypes of HAdVs.

The unusually high incidence of HAdV-3 in 2010 following a pandemic of influenza (H1N1) in 2009 might have had several causes. One possibility is there was a micro-environmental change in hosts following the pandemic era. As presented in this study, the outbreak caused by HAdV-3 following the pandemic era seemed not to be associated with specific changes in the viral *hexon* gene, which is known to encode major antigenic sites of HAdV. Instead, extensive changes in the overall host population's immune status resulting from the primary introduction of H1N1 influenza into the community could have mediated this unusually high incidence of HAdV. There was no significant changes were observed in the HAdV genome supports this hypothesis. The other possibility is that the original introduction of HAdV could lead to fluctuations in population immunity triennially, regardless of the influence of the influenza pandemic. During the preparation of this manuscript, repetitive HAdV outbreaks caused by HAdV-3 were also detected in 2013 (data not shown). Again, no significant mutations were observed using *hexon* sequence analysis targeting randomly sampled HAdV-3 viruses. This repetitive outbreak caused by the HAdV-3 suggests that when HAdV-3 was the major circulating virus, population immunity might have been diluted. Thus, newborn infants might be a newly susceptible group to HAdV-3 and this might have contributed to the triennial outbreak of HAdV-3 infection. To validate this hypothesis, a birth cohort-derived seroepidemiological study targeting specific antibodies against HAdVs should be carried out to test the present data further.

There are published data about the prevalence and distribution of HAdV serotypes in Korea [Kim et al., 2003; Lee et al., 2010a], but those descriptions are limited by being hospital based and not representative of the general Korean population. This study is believed to be the first nationwide report regarding an outbreak of HAdV infection based on the KINRESS data.

In conclusion, through a nationwide surveillance system during 2010 in Korea, this study has documented that in an outbreak of HAdV infection following a pandemic era, HAdV-3 was the predominant serotype based on the *hexon* gene. Further investigations to verify which factor(s) were associated with this abrupt outbreak following the H1N1 influenza virus pandemic in 2010 are needed to understand the major causes.

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