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BRIEF REPORT

Secular trend of genome types of respiratory adenovirus type 3 during 1983–2005: a study from Taiwan

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Abstract Genome type analysis of adenovirus type 3 (Ad3) in Taiwan identified four types (Ad3a, Ad3a2, Ad3a1, Ad3–7) during 1983–2005. Ad3a was the major type during 1983–1999, while Ad3a2 was the predominant type from 2001 to 2005. Phylogenetic analysis of the hexon gene of 23 isolates revealed that most Ad3a2 and Ad3–7 isolates belonged to one cluster, and most Ad3a isolates to the other cluster. The clinical manifestations included respiratory tract infections, acute gastroenteritis, hand-foot-and-mouth disease, febrile convulsion and pharyngoconjunctival fever. In conclusion, Ad3a2 has replaced Ad3a as the most common genome type in Taiwan since 2001.

Introduction

Adenovirus is a clinically important pathogen, causing 5–10% of lower respiratory tract infections in infants and young children [20]. There are 51 known human serotypes, which have been classified into six species (A–F). Only one-third of the 51 serotypes can cause human diseases. Species B (Ad3, 7, 14, 16, 21, 34, 35), species C (Ad1, 2, 5, 6), and species E (Ad4) are responsible for acute respiratory diseases in infants, young children, and military recruits [11, 12, 16, 21, 36, 38, 39]. The serotypes frequently recovered from children with respiratory tract infections are Ad1, Ad2, Ad3, Ad5 and Ad7 [20]. Among them, Ad3 accounted for 13% of respiratory infection in a survey of respiratory infections from 1967 to 1976 and is one of the most common causative agents of acute

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respiratory infections, pharyngoconjunctival fever (PCF) and conjunctivitis, with a worldwide distribution [2, 3, 14, 17, 18, 27, 30, 32, 33, 39].

At least 38 genome types of Ad3 have been identified worldwide. They include Ad3p (the prototype), Ad3p1–Ad3p3, Ad3a, Ad3a1–Ad3a18, Ad3b, Ad3b1, Ad3c–Ad3e, Ad3e1, Ad3e2, Ad3f–Ad3k, Ad3x and Ad3–7 [2–5, 13–16, 23, 29, 38]. The nomenclature system was proposed by Li and Wadell [23] and subsequently modified by Li et al. [19, 20, 24] based on the restriction fragment length polymorphism (RFLP) patterns. In Taiwan, adenoviruses are the second most common viral agent (4%), after RSV (7%) and followed by enterovirus (3%), in children hospitalized with respiratory infection [35]. With the exception of outbreaks due to Ad7 in 1999 and Ad4 in 2000 and 2001, Ad3 has existed as the most common serotype during the past two decades [25, 26]. However, the molecular epidemiology of Ad3 in Taiwan has only been reported in a study from northern Taiwan [6]. Ad3 genome types varied with time and geographic areas and were associated with different disease severity [14, 18, 19, 37]. To understand the prevalence and chronological change in genome types of Ad3 in Taiwan, we did genetic analysis of isolates from each year using RFLP for viral DNA genome typing and analysis of the nucleotide and amino acid sequence of the full hexon gene. Clinical characteristics of Ad3-infected patients were also studied in correlation with the Ad3 genome types.

Materials and methods

Adenovirus isolated from nasopharyngeal and eye specimens of patients visiting Kaohsiung Medical University Hospital from 1983 to 2005 were included for serotyping. Viruses were grown in HEp-2 or A549 cells for 3–5 days and identified by immunofluorescent assay using an adenovirus-specific monoclonal antibody (Chemicon, CA, USA). Virus stocks were prepared in HEp-2 cells with Eagle's minimum essential medium supplemented with 2% fetal calf serum and antibiotics.

Adenovirus serotypes were identified by PCR-RFLP as described in a previous report [31]. Viral DNA used for PCR-RFLP was extracted using a blood purification kit (Amershan Pharmacia Biotech Inc., NJ, USA). The primer pair AdnU-S' (5′-TTCCCCATGGCNCACAACAC-3′) and AdnU-A (5′-GCCTCGATGACGCCGCGGTG-3′) were used to amplify a 956-bp product from the hexon region. PCR products were subjected to digestion with three restriction enzymes, *Sty*I, *Hae*III and *Hin*fI (Promega, Madison, WI, USA), according to the manufacturer's instructions. The digested products were then electrophoresed on a 3% agarose gel containing ethidium bromide (0.5 μg/ml).

Viral DNA for RFLP analysis was extracted according to a previously reported method [25]. Briefly, the infected cells were lysed with SDS (1%) and digested with proteinase K (50 μg/ml) at 65°C for 1 h. DNA was extracted twice with phenol–chloroform-isoamyl alcohol (25:24:1) followed by RNase (100 μg/ml) treatment at 65°C for 30 min. Isolates identified as Ad3 by PCR-RFLP were subjected to RFLP analysis for genotyping. Aliquots containing 1–2 μg of viral DNA were digested with 10–15 U of *Bam*HI, *Hin*dIII, *Sma*I, *Xho*I, or *Bgl*I (Promega, Madison, WI, USA) according to the manufacturer's instructions. After enzyme digestion, viral DNA was electrophoresed on a 1% agarose gel containing ethidium bromide (0.5 μg/ml) for 16 h at 50 V. The RFLP patterns were identified according to the patterns of genome types reported previously [23, 26].

Four primers (AdHxF 5′-GCCGAGGCTGAGTTGC TTTCA-3′; AdHxR 5′-CGCTGGAGCCGTTTCCGGA C-3′; AdHxF-1, 5′-AACGTCTGATAACTCTCATG-3′; and AdHxR-1 5′-CAGTTGCGAGATGGGATGGA-3′) were used to amplify the full-length hexon gene sequence (2,835 bp). Products purified with QIAquick spin columns (Qiagen,Valencia, CA, USA) were used for sequencing.

For phylogenetic analysis, the hexon gene sequence data were analyzed using the DNASTAR Lasergene software (DNASTAR Inc., Madison, WI, USA). Phylogenetic analysis was conducted by the neighbor-joining method with MEGA 3 software (Molecular Evolutionary Genetics Analysis, Version 3.0) [22]. The robustness of the NJ tree was evaluated statistically by bootstrap analysis with 1,000 bootstrap samples. The demographics and the clinical characteristics of 65 patients for whom adequate information was available were analyzed.

Results

Ad3 accounted for 68 and 44% of adenovirus isolated during the periods of 1981–1989 and 1990–1998, respectively. Ad3 comprised of 36–81% of adenovirus isolated each year from 1999 to 2005. It was the most common serotype in the last two decades except in 1999 and 2001, when large outbreaks of Ad7 and Ad4, respectively, occurred.

Genome typing of Ad3 by RFLP

Ninety-two Ad3 isolates were randomly selected for genome type analysis. The number of isolates for genome typing for each time period is in proportion to the total amount of Ad3 in that time period, with the exception of the unusually large number in 2005 due to an epidemic outbreak [29]. Genome typing of Ad3 by full-genome RFLP identified four genome types, Ad3a, Ad3a1, Ad3a2

Table 1 Chronological change of Ad3 genome types during 1983–2005

	Genotype no. (%)			Total
	1983–1999	2000	2001–2005	
Ad3a	14 (53.8)	10 (47.6)	5 (11.1)	29 (31.5)
Ad3a1	1 (3.8)	0	0	1 (1.1)
Ad3a2	5 (19.2)	11 (52.4)	36 (80)	52 (56.5)
Ad3–7	6 (23.1)	0	4 (8.9)	10 (10.9)
Total	26	21	45	92

and Ad3–7 during 1983–2005. Ad3a predominated during the period of 1983–1999 (53%, 14/26), while Ad3a2 predominated in 2001–2005 (80%, 36/46) ($P \leq 0.001$) (Table 1). Both Ad3a and Ad3a2 were found in similar proportions in 2000 (48 vs. 52%). Ad3–7 was found sporadically in 1999 and 2003, while only one strain of Ad3a1 was found in 1983.

Comparison of nucleotide and amino acid sequences in the hexon region

Phylogenetic analysis showed that Ad3 isolates from 1983 to 2005 in our area grouped into two major clusters, which were separate from the prototype (GB strain, GenBank accession numbers X76549 and AY599834) and strains isolated from Korea. Cluster 1 consisted of most Ad3 isolates in 1983–1999, while Cluster 2 included most Ad3 isolates from 2001 to 2005 (Fig. 1). Three Chinese strains belonged to cluster 1 and the USA strain belonged to cluster 2. Unique nucleotides were found in cluster 1 and cluster 2 at seven positions: 614(T-G), 1,249(A-G), 1,285(A-G), 1,316(C-A), 1,731(T-C), 2,061(T-C), and 2,067(T-C), which led to changes in four amino acid residues: V205G, N417H, T429A, and A439D.

Clinical features of patients

The most common age of disease occurrence was 4 years old, and 79% were less than 7 years old. None of the cases had a fatal outcome. The ratio of males to females was 1.4:1. Twenty-five of the 65 patients (38.5%) had acute febrile pharyngotonsillitis. Lower respiratory tract infections such as acute bronchitis (29.2%, 19/65) and pneumonia (21.5%, 14/65) accounted for half of the cases. There was a higher percentage of Ad3a2 than of Ad3a (95.1 vs. 79.1%) in respiratory tract infections. Complications such as acute otitis media and acute sinusitis that made clinicians prescribe antimicrobial agents were found in 6 of 41 (14.6%) Ad3a2-infected patients, but not in any of the Ad3a cases. Acute gastroenteritis was found in 16.7% of Ad3a cases, but gastroenteritis did not occur in

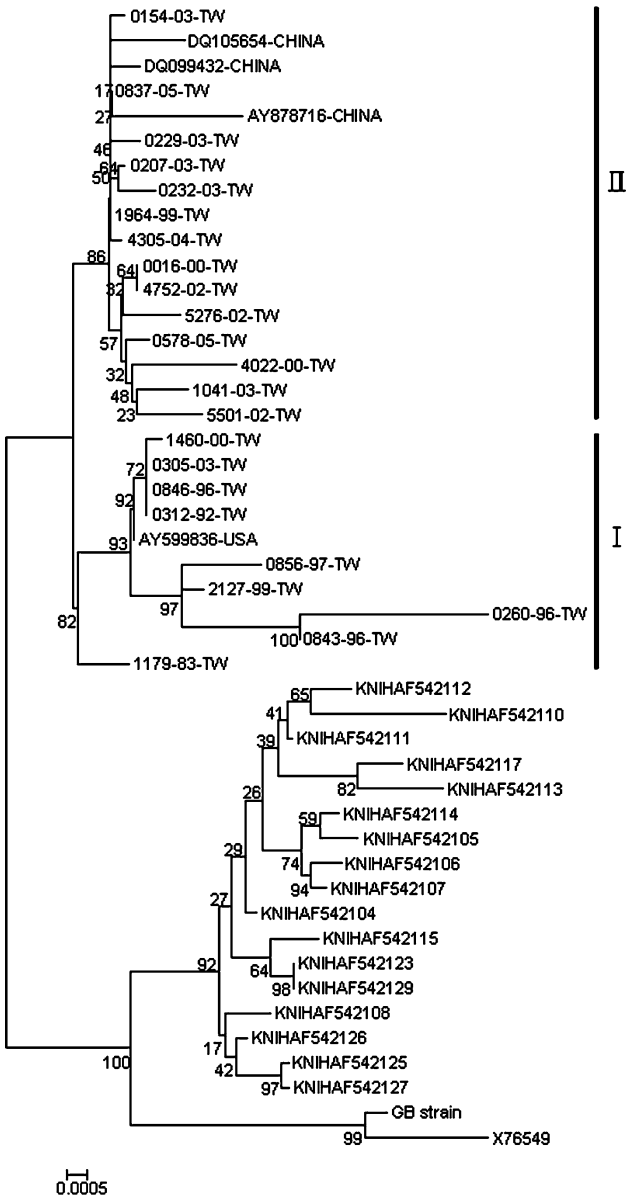

Fig. 1 Phylogenetic analysis of nucleotide sequences of full-length hexon genes of Ad3 isolates. The phylogenetic tree was constructed by the neighbor-joining method and using bootstrap analysis ($n = 1{,}000$) to determine the best-fitting tree. Sequences available in GenBank include Korean isolates whose names start with KNIH, Chinese isolates (AY878716, DQ099432, DQ105654), a USA isolate (AY599836), the prototype GB strain and X76549

Ad3a2-infected cases (p value $= 0.016$, Fisher's exact test) (Table 2).

Discussion

RFLP of the whole genome of adenovirus is a useful tool in molecular epidemiology [24]. A sequence library for adenoviruses typing was established in 2004 based on a 956-bp

Table 2 Clinical features of 65 Ad3-infected patients during 1992–2005

	Ad3a	Ad3a2	Total
Number of cases (%)	24 (36.9)	41 (63.1)	65 (100)
Age (years): median (range)	4 (0–9)	5 (0–63)	4 (0–63)
Male/female (ratio)	13/11 (1.18)	25/16 (1.56)	38/27 (1.41)
Clinical diagnosis [no.] (%)			
Acute pharyngotonsillitis[b] (%)	8 (33.3)	17 (41.5)	25 (38.5)
Acute bronchitis (%)	6 (25.0)	13 (31.7)	19 (29.2)
Pneumonia (%)	5 (20.8)	13 (31.7)	14 (21.5)
Acute gastroenteritis (%)	4 (16.7)	0 (0.0)	4 (6.2)
Other[a] (%)	1 (4.2)	2 (4.9)	3 (4.6)

[a] Hand-foot-and-mouth disease (2 cases) and febrile convulsion (1 case)

[b] One Ad3a and 2 Ad3a2 cases were pharyngoconjunctival fever

partial hexon sequence [34]. Nowadays, instead of the neutralization test, PCR-RFLP and sequence analysis of the partial hexon region are both important methods for epidemiological studies of adenovirus. Our phylogenetic study on the whole hexon gene had importance because serotype-specific epitopes are contained in the gene [8]. Phylogenetic analysis of the Ad3 hexon gene sequences among isolates from Taiwan revealed two clusters, and unique signatures of nucleotide and amino acid sequences were observed in different clusters of the hexon gene sequences. However, not every genome type uniquely belonged to a specific cluster by hexon gene analysis when comparing the hexon gene cluster result and the genome types (Fig. 1). Most Ad3a2 and Ad3–7 isolates were located in cluster 2 except the two Ad3a2 isolates from earlier years (isolate 312-92-TW from 1992 and isolate 846-96-TW from 1996), which belonged to cluster 1. Comparison of full hexon gene sequence analysis and human adenovirus serotypes in previous studies has revealed a discrepancy in grouping results in serotype 16, 50 (species B) and 51 (species D) [10]. The correlation of genome type and the result of phylogenetic analysis of the hexon gene for Korea Ad3 isolates showed that isolates of specific genome types were clustered in the phylogenetic tree [7]. In contrast, there was non-correlation between the results of genome typing and phylogenetic analysis on the hexon gene in our results.

The fact that Ad3a isolates that did not belong to cluster 1 were isolated both in 2004 and 2005 suggested there were nucleotides changes occurring in the hexon gene in the Ad3a genome type in the later years of our study period. Coincidentally, there was a community-derived outbreak of Ad3 in Taiwan in 2004 and 2005 [6]. The outbreak might be related to the fact that the hexon gene contains hypervariable regions, and the evolution of the adenovirus serotype is suggested to be driven by changes in the hypervariable regions of the hexon protein [9]. The changes of hexon gene nucleotides of Ad3a and Ad3a2 over time necessitates further observation, since fatal acute respiratory disease may be associated with variant-type adenoviruses, as exemplified by outbreaks of adenovirus serotype 14 in the USA in 2006–2007 [1]. Increasing numbers of cases of Ad3 have also been reported, with the identification of new genome types [20, 28].

Although there are 38 genome types of Ad3 in the world, only a few genome types occur in a specific geographic area. Chronological change in the genome type has been reported in specific geographic areas [20, 24]. Heterogeneity of genome types in an epidemic of Ad3 has been observed before [20]. Regarding the Ad3 genome types in the East Asia area, Ad3a2 was dominant, with occasional isolates of Ad3a4, Ad3a5 and Ad3a6 during the period from 1962 to 1988 in China [24]. In Japan, Ad3a was the predominant genome type, with occasional isolates of Ad3a8 and Ad3c from 1983 to 1991 [17]. For conjunctivitis manifestation in Japan, the predominant role of Ad3g was taken over by Ad3f during 1983–1986 [15]. In Korea, Ad3a13, Ad3a14, Ad3a15, Ad3a16, Ad3a17 and Ad3a18 were identified as new variants of Ad3a during the period of 1990–2000, and the dominant genome types were Ad3a16 and Ad3a13. Ad3 genome types in Korea are more diverse than those observed in China, Japan and Taiwan [13]. In this study, four genome types (Ad3a, Ad3a1, Ad3a2, Ad3–7) were identified in Taiwan. Ad3a was dominant during 1983–1999 and Ad3a2 was dominant in 2001–2005. Although Taiwan is a neighbor of China, Japan, and Korea and there is frequent traffic communication between these countries, different Ad3 genome type distributions were observed in the different countries.

Half of the Ad3a and Ad3a2 cases had a diagnosis of acute lower respiratory tract infection, such as pneumonia and bronchitis. While no gastroenteritis cases occurred among Ad3a2-infected patients, some Ad3a cases manifested mainly with acute gastroenteritis. Although Ad3 is not regarded as a gastroenteritis adenovirus like species F (Ad40 and Ad41), more than half of respiratory Ad3 infection cases may be accompanied by gastrointestinal discomfort symptoms [6]. Since some genome types may be associated with different disease presentations, as our results showed that clinical presentations of Ad3a and

Ad3a2 differed, the correlation of genome types and clinical manifestations will require a larger number of cases for confirmation.

In conclusion, we observed the genome type change of Ad3 in Taiwan from 1983 to 2005 with difference in clinical manifestations. Ad3a and Ad3a2 were the predominant genome types before and after 2000, respectively, with Ad3a1 and Ad3–7 being isolated occasionally.

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