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Cellular tropism and genetic stability of African pygmy hedgehog adenovirus 1 during serial passage

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Abstract

African pygmy hedgehog adenovirus 1 (AhAdV-1) was isolated from a hedgehog exhibiting respiratory symptoms in Japan. In this study, we evaluated the cellular tropism of AhAdV-1 using various mammalian cell lines and investigated its genetic stability during long-term serial passage in MDCK cells. AhAdV-1 exhibited high replication efficiency in MDCK, MDBK, CPK, and Vero cells but showed limited growth in BHK, HeLa, and HC11 cells. No replication was detected in RAW 264.7 and 3LL cells. Since MDCK cells demonstrated the highest viral production, serial passage was performed up to 110 passages. Whole-genome analysis revealed only four mutations, suggesting that AhAdV-1 is a genetically stable virus. These findings contribute to the understanding of the host range and evolutionary stability of AhAdV-1.

Key Words: African pygmy hedgehog adenovirus 1, Cellular tropism, Genetic analysis

Adenoviruses (AdVs) are viruses belonging to the family *Adenoviridae* within the order *Rowavirales*. They are classified into the genera *Mastadenovirus*, *Aviadenovirus*, *Atadenovirus*, *Siadenovirus*, and *Ichtadenovirus*[16)]. AdVs are icosahedral, non-enveloped viruses with diameters of approximately 65–90 nm[3,16,24)]. Their double-stranded DNA genomes range from 26 to 48 kbp and encode approximately 40 proteins. AdV capsids consist of 252 capsomeres, comprising 240 hexon and 12 penton base proteins. AdVs infect various vertebrates, and although many do not cause severe disease, they can be associated with clinical manifestations[20)]. In humans, AdVs are known to cause common colds[9)], and while 80% of pediatric AdV infections are mild, 20% result in pneumonia. In immunocompromised adults, AdV can cause lower respiratory tract infections[6,15)]. Additionally, AdVs, particularly *Human adenovirus* (HAdV) serotypes 8, 37, 53, 54, 56, and 64 of the HAdV-D species, are known etiological agents of epidemic keratoconjunctivitis[13,23)].

AdV infections are also significant in animals. Canine adenovirus (CAdV) types 1 and 2 cause infectious canine hepatitis and kennel cough, respectively[4,7,19)]. Bovine adenovirus type 7 (BAdV-7) was first isolated in Japan in 1965 from a cow with acute febrile illness, diarrhea, rhinitis, and conjunctivitis[12,18)]. Mouse adenovirus (MAdV-1) causes encephalitis, myocarditis, and

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respiratory infections in susceptible mice[1,8,11,25]. Skunk adenovirus (SkAdV-1) was isolated in Canada from skunks with acute respiratory disease and hepatitis[14]. SkAdV-1 has also been detected in deceased ferrets (*Mustela putorius*)[6], American porcupines (*Erethizon dorsatum*) and raccoons (*Procyon lotor*) with severe necrotizing bronchopneumonia[2], and pygmy marmosets (*Callithrix pygmaea*)[5].

In 2017, an outbreak of respiratory illness occurred among 24 African pygmy hedgehogs in Japan, with 15 exhibiting symptoms such as nasal discharge, congestion, sneezing, coughing, and respiratory distress. During the outbreak, five hedgehogs died following the onset of respiratory symptoms. Pathological examination revealed no macroscopic lesions in the upper respiratory tract; however, one case showed significant lesions in the lower respiratory tract, with pulmonary edema, firm dark red lung lobes, and hemorrhagic pleural effusion. A novel AdV was isolated from a throat/nasal swab of infected hedgehog using Madin-Darby canine kidney (MDCK) cells in previous our studies[17,21]. Whole-genome sequencing identified the virus as African pygmy hedgehog adenovirus 1 (AhAdV-1, Accession: MK937781.1)[17]. AhAdV-1 belongs to the genus Mastadenovirus within the family *Adenoviridae* and has a 31,764-bp genome encoding 30 open reading frames (ORFs) and 13 structural proteins[21]. The AhAdV-1 genome is 84 bp shorter than that of SkAdV-1, with a sequence identity of 99.7%. Previously, we analyzed the replication dynamics, cytopathic effects (CPE), activation of the MAPK signaling pathway, and its impact on viral replication of AhAdV-1 in MDCK cells[26]. AhAdV-1 efficiently replicated and induced apoptosis accompanied by caspase-3 activation within 24 hours post-infection. In infected cells, activation of p38 MAPK, Akt, and ERK1/2 was observed as early as 3 hours post-infection, while phosphorylation of SAPK/JNK was detected at 24 hours post-infection. Inhibition of p38 MAPK suppressed viral replication, suggesting that AhAdV-1 may utilize the p38 pathway for its replication.

Previous studies have reported cases of SkAdV-1 and other closely related adenoviruses infecting different animal species[14], suggesting that AhAdV-1 may exhibit similar properties. Although adenoviruses are generally considered genetically stable, the impact of prolonged serial passage on their mutation accumulation has not been extensively studied. This study aimed to clarify the cellular tropism of AhAdV-1 by evaluating its replication characteristics in various mammalian cell lines and analyzing the presence of genetic mutations during long-term serial passage. This investigation provides insights into the host range and evolutionary characteristics of AhAdV-1 and may contribute to the risk assessment of future zoonotic adenovirus infections.

To determine the cellular tropism of AhAdV-1, its replication efficiency was evaluated in 10 different mammalian cell lines. The following cell lines were used: MDCK, Madin-Darby bovine kidney (MDBK), African green monkey kidney (Vero), Porcine kidney (CPK), Crandell-Rees feline kidney (CrFK), Human epithelial carcinoma (HeLa), and Baby hamster kidney (BHK) cells. These cell lines were cultured in Dulbecco's modified Eagle medium-high glucose (DMEM; Wako, Osaka, Japan) supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine (Gibco, Tokyo, Japan), and 10,000 U/mL penicillin-streptomycin (Wako, Osaka, Japan). Murine breast epithelial cells (HC11) were cultured in DMEM supplemented with 5 μg/mL insulin (Wako, Osaka, Japan), 10% FBS, 200 mM L-glutamine, 10,000 U/mL penicillin-streptomycin, and 1 mM GlutaMAX (Gibco, Tokyo, Japan). Murine leukemia macrophage cells (RAW 264.7) and murine lung cancer cells (3LL) were maintained in RPMI 1640 (Nacalai, Kyoto, Japan) supplemented with 10% FBS, 200 mM L-glutamine, and 10,000 U/mL penicillin-streptomycin. These cell lines were seeded in 12-well culture plates and incubated until reaching 60% confluency under conditions of 37°C and 5% CO_2. At this stage, the culture medium was replaced with DMEM containing 2% FBS, and AhAdV-1 infection was performed. AhAdV-1 virus stock was prepared using MDCK cells and used to infect target cells at a multiplicity of infection (MOI) of 0.1. The viral

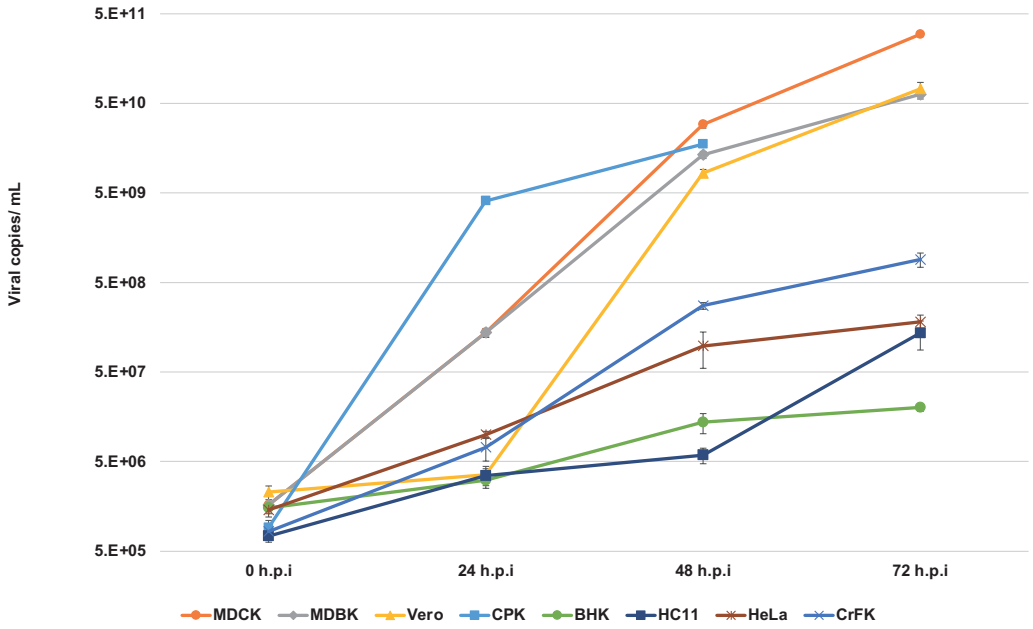

Fig. 1. Growth Kinetics of AhAdV-1 in Various Mammalian Cell Lines
AhAdV-1 was inoculated into MDCK, MDBK, Vero, CPK, BHK, HC11, HeLa, and CrFK cells at an MOI of 0.1. Culture supernatants were collected at 1, 24, 48, and 72 hours post-infection. Viral DNA levels were quantified by real-time PCR (n = 4).

load of AhAdV-1 in the culture supernatant was quantified by real-time PCR (n = 4).

For real-time PCR analysis, AhAdV-1 DNA polymerase was targeted using the following primers: AhAdV-1 inner-F primer (5'-CCGTACA GGGCGTTAGATAATAA-3'), AhAdV-1 inner-R primer (5'-GGAAGTGCTTAGCCAGAGAATA-3'), and AhAdV-1 probe (5'-/56-FAM/TTTGGCCTG/ ZEN/GATGTTGAGTTGCAC-3'). The PCR reaction mixture consisted of 10 µL Probe qPCR Mix (Takara Bio, Shiga, Japan), 5 µL nuclease-free water, 1 µL forward primer, 1 µL reverse primer, 1 µL probe, and 2 µL sample DNA, making a total volume of 20 µL. Real-time PCR was performed using the MyGo Pro System (Novacyt, Eastleigh, UK) under the following conditions: 95°C for 30 seconds (holding), followed by 45 cycles of amplification at 95°C for 10 seconds, 53°C for 20 seconds, and 72°C for 20 seconds. As a positive control for real-time PCR, cDNA amplified using the AhAdV-1 outer-F primer (5'-GCCGGACGCTATCTTTAAT-3') and AhAdV-1 outer-R primer (5'-CCCACTTACATTGGCATCTACT-3') was used. The PCR reaction mixture for gene amplification included 12.5 µL Go Taq Green Master Mix (Promega, Madison, WI, USA), 8.5 µL nuclease-free water, 1 µL forward primer, 1 µL reverse primer, and 2 µL sample DNA, for a total of 25 µL. PCR amplification was conducted using a T100 Thermal Cycler (BIO-RAD, Hercules, CA, USA) under the following conditions: 95°C for 180 seconds (holding), followed by 35 cycles at 95°C for 30 seconds, 52°C for 30 seconds, and 72°C for 40 seconds. Nuclease-free water was used as the negative control.

Cytopathic effects (CPE) were observed in all cell lines except RAW 264.7 and 3LL cells, coinciding with viral replication (data not shown). Quantification of viral gene expression by real-time PCR revealed that among all tested cell lines, AhAdV-1 exhibited the highest replication efficiency in MDCK, CPK, MDBK, and Vero cells (Fig. 1). In CPK cells, the highest viral titer (1.74×10^{10} copies/mL) was detected at 48 hours post-infection. Although Vero cells exhibited the lowest viral titer among the four highly permissive cell lines at 24 hours post-infection, the viral titer

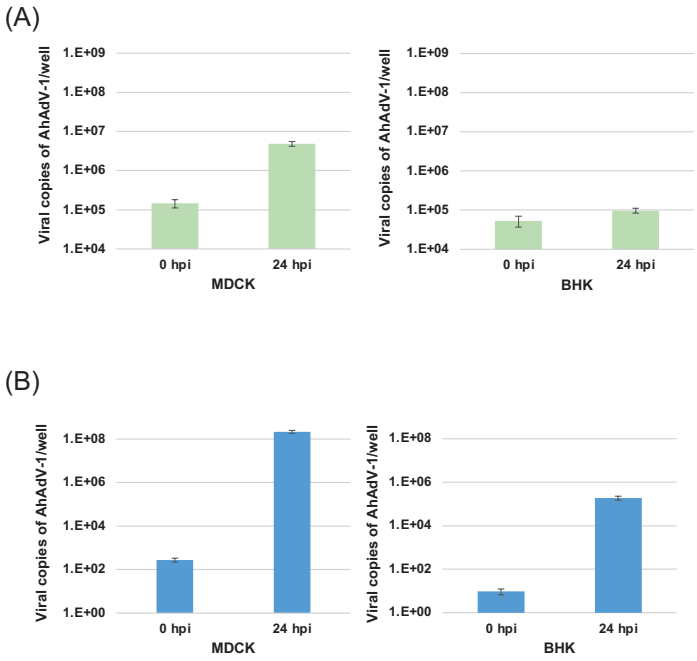

Fig. 2. Intracellular Viral Replication of AhAdV-1 in MDCK and BHK Cells
AhAdV-1 was inoculated into MDCK (n = 6) and BHK (n = 6) cells at an MOI of 0.1. Infected cells were collected at 1 hour and 24 hours post-infection. Viral copy numbers were quantified by real-time PCR. (A) shows the detection of intracellular AhAdV-1 DNA, while (B) shows the detection of intracellular AhAdV-1 mRNA.

peaked at 72 hours post-infection, reaching 7.25×10^{10} copies/mL. MDCK cells exhibited the highest viral titer of 3.0×10^{11} copies/mL at 72 hours post-infection. Since nearly all CPK cells exhibited CPE at 48 hours, viral titers at 72 hours were not evaluated. In contrast, HC11, HeLa, CrFK, and BHK cells exhibited lower susceptibility to AhAdV-1 than the four highly permissive cell lines. CrFK cells reached a maximum viral titer of 9.0×10^{8} copies/mL at 72 hours post-infection, the highest among the low-permissive cell lines. Conversely, BHK cells had the lowest viral titer of 2.0×10^{7} copies/mL at 72 hours post-infection among the low-permissive cell lines. No viral replication was detected in RAW 264.7 and 3LL cells (data not shown).

To further assess the replication efficiency of AhAdV-1, we compared the intracellular viral DNA and mRNA levels in MDCK and BHK cells at 0 and 24 hours post-infection at an MOI of 0.1 (Fig. 2). Intracellular DNA quantification revealed that at 1 and 24 hours post-infection, MDCK cells contained 1.47×10^{5} copies/well and 4.88×10^{6} copies/well, respectively, whereas BHK cells contained 5.34×10^{4} copies/well and 9.77×10^{4} copies/well, respectively. Similarly, intracellular mRNA quantification at 1 and 24 hours post-infection showed that MDCK cells contained 2.78×10^{2} copies/well and 2.16×10^{8} copies/well, respectively, whereas BHK cells contained 9.53×10^{1} copies/well and 1.89×10^{5} copies/well, respectively. These results indicate that AhAdV-1 replicates and propagates efficiently in MDCK cells.

Due to the high viral titers observed in MDCK cells, this cell line was used for long-term serial passage. The virus was serially passaged for a total of 110 passages, and whole-genome analysis was performed using next-generation sequencing (NGS) to assess genetic mutations. MDCK cells were seeded into 24-well tissue culture plates and infected with AhAdV-1 when they reached 100% confluency. In the initial infection, AhAdV-1 isolated from an infected hedgehog was serially diluted tenfold across nine wells before being used to infect MDCK cells. The supernatant from the

Table 1. Serial Passaging and Genomic Mutations of AhAdV-1

Position (MK937781.1)	25,348 - 25,353																									27,580					31,638			
	25,348					25,349					25,350					25,351					25,352					25,353									
Referense Seq.	A					T					T					A					C					T					C					A			
Passage No.	Number of reads					Number of reads					Number of reads					Number of reads					Number of reads					Number of reads					Number of reads					Number of reads			
	–	A	C	G	T	–	A	C	G	T	–	A	C	G	T	–	A	C	G	T	–	A	C	G	T	–	A	C	G	T	A	C	G	T	A	C	G	T
0	1	4,020	2	4	2	1	0	0	6	4,141	1	3	2	5	4,164	1	4,146	5	1	0	1	2	4,169	1	2	1	3	0	5	4,174	0	3	3,651	0	1	443	14	0	0
10	9	989	0	3	1	9	1	3	3	1,028	9	0	0	2	1,043	9	1,038	2	3	0	9	4	1,046	0	1	9	0	0	3	1,052	0	1	323	1	569	105	1	0	0
24	Deletion (25348-25353)																									0	1	3	3	642	54	6	0	0				
30	Deletion (25348-25353)																									0	1	2	1	1,043	81	14	0	0				
40	Deletion (25348-25353)																									0	0	0	2	2,180	218	20	0	0				
50	Deletion (25348-25353)																									0	2	4	2	5,996	653	45	0	0				
60	Deletion (25348-25353)																									0	0	0	0	255	0	1	0	0				
70	Deletion (25348-25353)																									0	3	2	1	3,541	0	57	0	0				
80	Deletion (25348-25353)																									0	1	2	2	2,939	2	41	0	1				
90	Deletion (25348-25353)																									1	3	1	1	2,522	0	23	0	1				
110	Deletion (25348-25353)																									0	0	0	1	1,211	0	20	1	0				
Amino acid substitution/ deletion (Protein)	Thr and Ile deletions (E3 putative 12.5K)																									Ala→Val (Fiber)					*Non-coding region*						

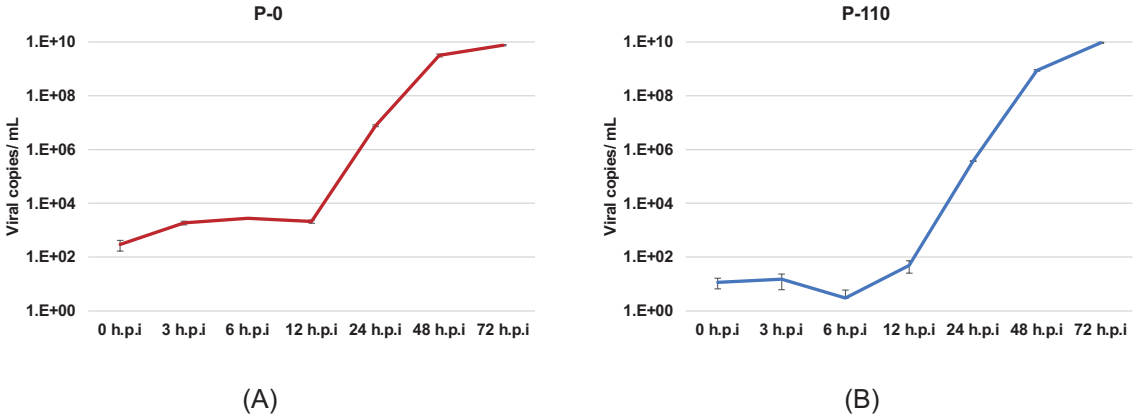

Fig. 3. One Step Growth of P-0 and P-110 AhAdV-1
The AhAdV-1 was serially passaged 110 times in MDCK cells at an MOI of 0.1, and Viral DNA levels of P-0 (A) and P-110 (B) viruses were quantified by real-time PCR (n = 4).

final well exhibiting CPE was then used to infect fresh MDCK cells. Serial passage was conducted every five days. Samples were collected every ten passages, and the full-length AhAdV-1 genome was sequenced using the MiSeq System (Illumina, California, USA). The obtained sequences were analyzed using the CLC Genomics Workbench (QIAGEN, Hilden, Germany). Sequence reads from each sample were mapped against the reference sequence (MK937781.1), and the number of reads and base composition were calculated. The read mapping data was compared between passages using the Basic Variant Detection command in the CLC software to identify the mutation sites.

As shown in Figure 3 and Table 1, in the 37°C culture group, we analyzed passages 10 (P-10), P-24, P-30, P-40, P-50, P-60, P-70, P-80, P-90, and P-110. The results revealed that from P-10 onward, a C-to-T substitution at nucleotide position 27,580 bp resulted in an amino acid substitution from alanine (Ala) to valine (Val) at position 211 of the Fiber protein. Additionally, from P-24 onward, a six-nucleotide deletion at positions 25,348 bp–25,353 bp led to the loss of two amino acids, threonine (Thr) and isoleucine (Ile), in the E3 putative 12.5K protein. Furthermore, in the non-coding region at P-70, an A-to-C substitution was observed at nucleotide position 31,638 bp; however, this did not result in an amino acid substitution. Interestingly, we observed a phenomenon in which specific mutations accumulated progressively with serial

passaging, and once a mutation became fixed in all viral genomes, a subsequent mutation would emerge. Genomic mutations acquired during serial passaging of AhAdV-1 up to passage 110 were primarily detected in the Fiber and E3 putative 12.5K proteins. The Fiber protein of adenoviruses binds to cellular receptors, suggesting that Fiber mutations may impact viral infectivity. However, no differences were observed one step growth and cytopathic effects between P-0 and P-110 AhAdV-1 (Fig. 3). To clarify the reasons, it will be necessary to identify the cellular receptor for AhAdV-1, conduct binding assays between the Fiber protein and the receptor, and perform structural analyses of the mutated Fiber proteins. The E3 putative 12.5K protein does not affect viral replication in cell culture but is considered important in vivo[10]. Our analysis of AhAdV-1 up to passage 110 identified only four mutations, suggesting that AhAdV-1 exhibits a remarkably slow mutation rate in cultured cells. We are currently conducting further analyses to elucidate the molecular basis by which these mutations affect viral growth ability. SkAdV-1 shares high sequence homology with BtAdV and CAdV[14], and AhAdV-1 exhibits approximately 99.7% genomic homology with SkAdV-1[17,21]. Further analyses are required which virus is original; however, our findings suggest that AhAdV-1 may undergo gradual evolution over time.

In this study, we demonstrated that AhAdV-1 exhibits broad cell tropism across various animal-derived cultured cells and efficiently propagates in MDCK cells. Moreover, even after long-term serial passaging, the genetic mutations remained minimal, indicating that AhAdV-1 is a genetically stable virus with a slow evolutionary rate.

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Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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