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Genetic characteristics of the isolate of human adenovirus type 55 (*Adenoviridae*: *Mastadenovirus)* isolated in Moscow in 2022

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Abstract

Introduction. Adenovirus infection occurs globally in the form of sporadic cases and isolated outbreaks. Human adenovirus type 55 (HAdV-55), endemic in China and South Korea, causes acute respiratory viral infections (ARVI) of varying severity, both among the civilian population and in military units in different countries of the world. Genomic research facilitates reliable identification of HAdV-55.

The aim of this study was to identify HAdV isolated in Moscow in 2022, as well as to conduct whole-genome sequencing and comparative genomic research.

Materials and methods. HAdV-55 was isolated from a sample of a patient hospitalized with pneumonia and analyzed using restriction fragment length polymorphism analysis and whole-genome sequencing. Bioinformatics comparative analysis was performed on a sample of sequences of 83 isolates.

Results. The whole-genome sequencing of first isolated in Russia HAdV-55 was conducted. The sequence of isolate SCV3008:Ad55 was deposited in GenBank (Accession Number PQ641625). Unique mutations in the SCV3008:Ad55 genome were identified, one of which resulted in a conservative T29A substitution in the penton that did not affect its functions. Phylogenetic analysis showed clustering of SCV3008:Ad55 with isolates of clade II, which included representatives of 7 countries on different continents, indicating a wide distribution of HAdV-55. Isolates from endemic regions of China and South Korea formed separate clades. The study of microsatellite length polymorphism in untranslated regions of the genome became an additional tool for distinguishing closely related genomes.

Conclusion. The obtained genomic information laid the foundation for further monitoring for HAdV-55 in Russia and demonstrated the informativeness and significance of whole-genome studies for monitoring adenoviruses. The development and implementation of genotyping methods aimed at detecting HAdV-55 and other clinically relevant genotypes will significantly improve the effectiveness of the diagnosis of adenovirus infections with the threat of developing bronchopneumonia.

Keywords: *human adenovirus type 55; HAdV-55; whole-genome sequencing; phylogenetic analysis*

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
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Генетическая характеристика изолята аденовируса человека 55-го генотипа (*Adenoviridae*: *Mastadenovirus)*, выделенного в Москве в 2022 г.

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Резюме

Введение. Аденовирусная инфекция встречается повсеместно в виде спорадических случаев и отдельных вспышек. Аденовирус человека 55-го генотипа (HAdV-55), эндемичный для территорий Китая и Южной Кореи, вызывает острые респираторные вирусные инфекции (ОРВИ) разной степени тяжести как среди гражданского населения, так и в воинских коллективах в разных странах мира. Геномные исследования способствуют достоверной идентификации HAdV-55.

Цель данной работы состояла в идентификации HAdV, выделенного в Москве в 2022 г., проведении полногеномного секвенирования и сравнительного геномного исследования.

Материалы и методы. HAdV-55 выделили из образца пациента, госпитализированного с пневмонией, исследовали методами анализа полиморфизма длины рестрикционных фрагментов и полногеномного секвенирования. Биоинформационный сравнительный анализ выполнили для выборки геномов 83 изолятов.

Результаты. Проведено полногеномное секвенирование изолята HAdV-55, впервые выделенного в РФ. Последовательность генома изолята SCV3008:Ad55 депонировали в GenBank (регистрационный номер PQ641625). Выявлены уникальные мутации в геноме SCV3008:Ad55, одна из которых приводила к консервативной замене T29A в пентоне, не влияющей на его функции. Филогенетический анализ показал кластеризацию SCV3008:Ad55 с изолятами клады II, включившей представителей 7 стран разных континентов, что свидетельствует о широком распространении HAdV-55. Изоляты эндемичных регионов Китая и Южной Кореи формировали отдельные клады. Исследование полиморфизма длин микросателлитов в нетранслируемых областях генома стало дополнительным инструментов различения близкородственных геномов.

Заключение. Сравнительное геномное исследование изолятов HAdV-55, появившегося в результате рекомбинации HAdV-14 и HAdV-11, показало медленное накопление мутаций с 1969 г. как в транслируемых, так и в нетранслируемых областях, позволило выявить уникальные замены нового изолята SVC3008:Ad55. Полученная геномная информация заложила основу для дальнейшего мониторинга HAdV-55 в России и продемонстрировала информативность и значимость полногеномных исследований для наблюдения за аденовирусами. Разработка и внедрение в практику методов генотипирования, нацеленных на выявление HAdV-55 и других клинически значимых генотипов, позволит значительно повысить эффективность диагностики аденовирусных инфекций с угрозой развития бронхопневмонии.

Ключевые слова: *аденовирус человека 55-го генотипа; HAdV-55; полногеномное секвенирование; филогенетический анализ*

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Introduction

Adenoviruses (family *Adenoviridae*) are non-enveloped, double-stranded DNA viruses, classified into 6 genera: *Aviadenovirus*, *Barthadenovirus*, *Ichtadenovirus*, *Mastadenovirus*, *Siadenovirus* and *Testadenovirus*. Mammalian adenoviruses belong to the genus *Mastadenovirus*, which includes more than 50 species. Human adenoviruses (HAdV) belong to 7 species: *Mastadenovirus adami*, *M. blackbeardi*, *M. caesari*, *M. dominans*, *M. exoticum*, *M. faecale* and *M. russelli*[1]. Different types of HAdV have varying tissue tropism, which often correlates with specific clinical symptoms of the infection [1]. HAdV primarily cause acute respiratory viral infections (ARVI), but can also affect the eyes, intestines, urinary tract and nervous system. The severity of the disease depends on the type of virus and the host's immune status [1–5]. The most severe respiratory infections are caused by HAdV 8 genotypes out of 10 belonging to the *M. blackbeardi* species: 3, 7, 11, 14, 16, 21, 50, 55 [6].

The history of isolating HAdV-55 as a separate genotype demonstrates the role and development of the methodological base of virology, contributing to a more accurate classification of viruses. For the first time, the atypical HAdV-11 virus as a pathogen of ARVI was identified using immunochemical methods in 1974 [7]. In 1991, the comparison of DNA fragment length polymorphism of isolates allowed the identification of the HAdV-11a genotype and demonstrated that viruses of this genotype are associated with upper respiratory tract infections and bronchopneumonia [8]. In 2009, the first complete genome of the HAdV-11a isolate HAdV11-QS (registration number FJ643676) was published, obtained by assembling overlapping amplicons after Sanger sequencing. Comparison of sequencing data contributed to the demonstration of the origin of HAdV-11a through recombination: the HAdV-11a genome is based on the HAdV-14 genome and part of the hexon gene of HAdV-11 [9]. In 2011, the Human Adenovirus Working Group recommended using full-genome sequences for typing and characterizing HAdV and classifying recombinants into new genotypes based on differences in nucleotide sequences and biological properties [10]. Based on these recommendations, in 2013, the recombinant HAdV-11a was named HAdV-55 with the prototype isolate HAdV11-QS [11]. Retrospective studies of collection isolates have shown that HAdV-55 is endemic to China and South Korea and dominated among viruses isolated during ARVI in Beijing from 1965 to 1985 [8]. Outbreaks of HAdV-55 ARVI in organized groups have been recorded since 1969 among military personnel in Spain [7], in a vocational training center in the USA [12], among children in Argentina, Chile and Uruguay [13], in psychiatric institutions in Israel [14], and in family groups in China [15]. HAdV-55, compared to respiratory adenoviruses of other genotypes, causes more severe diseases and poses a significant threat to public health [6]. In Russia, according to data from the Center for Ecology and Epidemiology of Influenza at the D.I. Ivanovsky Institute of Virology, N.F. Gamaleya NRCEM of the Ministry of Health of Russia, in collaboration with 10 reference bases, during the epidemic season of 2021–2022, the frequency of positive adenovirus samples in the studied areas was 7.7% (1793 samples) out of those tested for ARVI [16]. HAdV, isolated from one of the 1793 samples, became the subject of detailed study.

The aim of the study is the identification of HAdV isolated in Moscow in 2022, as well as conducting whole-genome sequencing and comparative genomic study.

Materials and methods

Materials. Bronchoalveolar lavage (BAL) from a hospitalized 34-year-old man with a diagnosis of unspecified pneumonia. The study was conducted with the voluntary informed consent of patients. The study protocol was approved by the Ethics Committee of the Moscow State Medical University «Infectious Clinical Hospital No. 1 of the Moscow Department of Health» (Protocol No. 8 dated 12/28/2022).

Methods. *The identification of viruses* was carried out by extracting RNA/DNA from clinical material using the RIBO-PREP kit (Interlabservice, Russia) followed by the detection of RNA/DNA of respiratory infection pathogens in real-time reverse transcription polymerase chain reaction (RT-PCR) using AmpliSens ARVI-screen-FL commercial test systems (Interlabservice, Russia) according to the manufacturer's instructions on the Bio-Rad CFX-96 detection amplifier (Bio-Rad, USA).

Isolation of HAdV. The virus was accumulated in HEK293 cells (human embryonic kidney): 100 µL of BAL was used to infect the cells (0.5×10^6 cells/3 cm², incubated under standard conditions (+37 °C, 5% CO_2) until cytopathic effect (CPE) occurred. For the preparative amplification of the virus, 15 cm diameter culture dishes were used. Infected cells were collected after reaching 100% CPE, concentrated by low-speed centrifugation (2000 rpm/10 min), re-suspended in buffer (0.01 M Tris-HCl pH 8.0, 0.01 M NaCl, 5 mM EDTA), subjected to three freeze-thaw cycles, and centrifuged at 5000 rpm/10 min, with the pellet being discarded. The adenovirus was purified from the supernatant using ultracentrifugation in a cesium chloride density gradient (in stepwise (CsCl with refractive indices of 1.355, 1.365, and 1.375) and equilibrium gradient (CsCl with a refractive index of 1.365)).

Analysis of restriction fragment length polymorphism (RFLP). Genomic DNA from the purified virus was extracted using the Wizard Genomic DNA Purification Kit (Promega, USA). DNA (1 µg) was hydrolyzed with the restriction enzymes Cfr41I, XagI and XhoI (Thermo, USA) and analyzed by agarose gel electrophoresis, using a longer incubation period to detect low molecular weight fragments. *In silico* analysis of RFLP was conducted using the Geneious Prime software (Biomatters, New Zealand).

Sequencing and genome assembly. Library preparation was performed using the KAPA HyperPlus Kit

[1] ICTV. Family: Adenoviridae. Available at: https://ictv.global/report/chapter/adenoviridae/adenoviridae

Table 1. HAdV-55 strains used for genomic analysis in order to study the spread of the virus, regional persistence and genetic variability
Таблица 1. Штаммы HAdV-55, используемые для геномного анализа с целью изучения распространения вируса, региональной персистенции и генетической изменчивости

GenBank Accession Number Номер в базе NCBI	Country Место выделения	Year of isolation Год выделения	GenBank Accession Number Номер в базе NCBI	Country Место выделения	Year of isolation Год выделения
MN654381.1	Egypt / Египет	2000	PP002035.1	China / Китай	2018
MN654383.1	Egypt / Египет	2000	PP002036.1	China / Китай	2018
MN654385.1	Egypt / Египет	2000	PP002037.1	China / Китай	2018
MN654380.1	Egypt / Египет	2000	PP002043.1	China / Китай	2018
MN654382.1	Egypt / Египет	2002	PP002044.1	China / Китай	2018
MN654390.1	Egypt / Египет	2005	PP002045.1	China / Китай	2018
MN654391.1	Egypt / Египет	2005	PP002046.1	China / Китай	2018
MN654386.1	Egypt / Египет	2007	MH256653.1	China / Китай	2018
MN654384.1	Egypt / Египет	2008	MH256655.1	China / Китай	2018
MN654387.1	Egypt / Египет	2009	MH256657.1	China / Китай	2018
MG905110.1	Spain / Испания	1969	MH256654.1	China / Китай	2018
FJ643676.1	China / Китай	2006	MH256656.1	China / Китай	2018
JX123027.1	China / Китай	2010	PP002040.1	China / Китай	2018
JX491639.1	China / Китай	2011	MT806174.1	China / Китай	2019
JX123028.1	China / Китай	2011	MT806175.1	China / Китай	2019
MK123979.1	China / Китай	2011	MT806170.1	China / Китай	2019
KJ883522.1	China / Китай	2011	MT806172.1	China / Китай	2019
KP279748.1	China / Китай	2012	MT806173.1	China / Китай	2019
KP896478.1	China / Китай	2012	MT806171.1	China / Китай	2019
JX123029.1	China / Китай	2012	OM714808.1	China / Китай	2020
KC857701.1	China / Китай	2012	OP375144.1	China / Китай	2021
KP896483.1	China / Китай	2013	MN654388.1	Singapore / Сингапур	2005
KJ883520.1	China / Китай	2013	MN654389.1	Singapore / Сингапур	2005
KJ883521.1	China / Китай	2013	MN654394.1	США / USA	1976
KP896484.1	China / Китай	2013	MN654392.1	США / USA	1997
MK123980.1	China / Китай	2013	MT513753.1	США / USA	2006
MK123981.1	China / Китай	2013	MN654395.1	США / USA	2020
KF908851.1	China / Китай	2013	MN654375.1	South Korea / Южная Корея	2009
MK886831.1	China / Китай	2015	MN654376.1	South Korea / Южная Корея	2009
KX289874.1	China / Китай	2015	MN654377.1	South Korea / Южная Корея	2009
KY070248.1	China / Китай	2016	MN654378.1	South Korea / Южная Корея	2009
KY780931.1	China / Китай	2016	MN654379.1	South Korea / Южная Корея	2009
KY780932.1	China / Китай	2016	KX494979.1	South Korea / Южная Корея	2016
KY780933.1	China / Китай	2016	KY471318.1	South Korea / Южная Корея	2017
PP002039.1	China / Китай	2018	KY471322.1	South Korea / Южная Корея	2017
PP002041.1	China / Китай	2018	KY471319.1	South Korea / Южная Корея	2017
MN052861.1	China / Китай	2018	KY471320.1	South Korea / Южная Корея	2017
MK123978.1	China / Китай	2018	KY471321.1	South Korea / Южная Корея	2017
PP002033.1	China / Китай	2018	KY471323.1	South Korea / Южная Корея	2017
PP002034.1	China / Китай	2018	MW053454.1	South Korea / Южная Корея	2019
PP002038.1	China / Китай	2018	MN654393.1	Japan / Япония	2012
PP002032.1	China / Китай	2018			

(F. Hoffmann-La Roche Ltd., Switzerland) according to the manufacturer's protocols, quality and size checks of the libraries were conducted using electrophoresis on High Sensitivity DNA Chips 2100 Bioanalyzer System (Agilent, USA), sequencing was carried out on the NextSeq 500/550 (Illumina, USA) instrument using Mid Output 300 cycles cartridges. For de novo assembly and reference sequence assembly, we used the CLC Genomic Workbench v. 21 software package (Qiagen, USA). To refine the sequences of homopolymers, Sanger sequencing was performed, using the BDT UltraSeq HP Kit (SenseCare Bio, China), with electrophoresis conducted in 50 cm capillaries in POP-7 gel on the 3500 Genetic Analyzer (Applied Biosystems, USA).

Comparative analysis. The comparative analysis included 83 complete genomes of HAdV-55 (**Table 1**) and the genome of HAdV-14 (MF062484). The alignment of genomic sequences of the isolate samples, the construction of the Neighbor-joining phylogenetic tree, and the calculation of ANI (average nucleotide identity) were performed using the Whole Genome Alignment module of the CLC Genomic Workbench v. 21 software package (Qiagen, USA). The MEGA11 program was used for tree visualization, as well as translation of reading frames and alignment of amino acid sequences [17].

Results

In a sample of respiratory specimens received from hospitals in Moscow during the 2021–2022 season, 12 contained HAdV according to qPCR data. The samples were analyzed for viral load values and the multiplicity of infection. One of the samples (bronchoalveolar lavage fluid from a patient hospitalized with pneumonia), characterized by a high level of HAdV DNA load (cycle threshold value, Ct = 12.3) and the absence of co-infection with other respiratory viruses, was used for HAdV isolation.

The isolated adenovirus was identified as HAdV-55 based on sequencing data, deposited in the State Collection of Viruses at the D.I. Ivanovsky Institute of Virology of the N.F. Gamaleya NRCEM of the Ministry of Health of Russia under the number SCV3008:Ad55, and the genomic data were registered in GenBank (registration number PQ641625).

RFLP analysis of the isolate DNA revealed the following fragments: Cfr41I (12894, 8674, 7768, 2664, 1194, 1181 and 403 bp), XhoI (10335, 8005, 6544, 5761, 2628, 1355, and 150 bp) and XagI (20615, 5219, 3789, 2944, 1359 and 852 bp). **Fig. 1** (*a*) presents the most prominent of them. Comparison with *in silico* data for isolates HAdV-55 (MG905110), HAdV-11 (AY163756) and HAdV-14 (MF062484) (Fig. 1 *b*) confirms the similarity of the restriction fragments of isolates SCV3008:Ad55 and HAdV-55 (MG905110) and emphasizes that the genome of the recombinant HAdV-55 is primarily composed of HAdV-14 genes.

The similarity with HAdV-14 was also demonstrated by the ANI calculation between the genomes of the HAdV-55 samples presented in Table 1, SCV3008:Ad55,

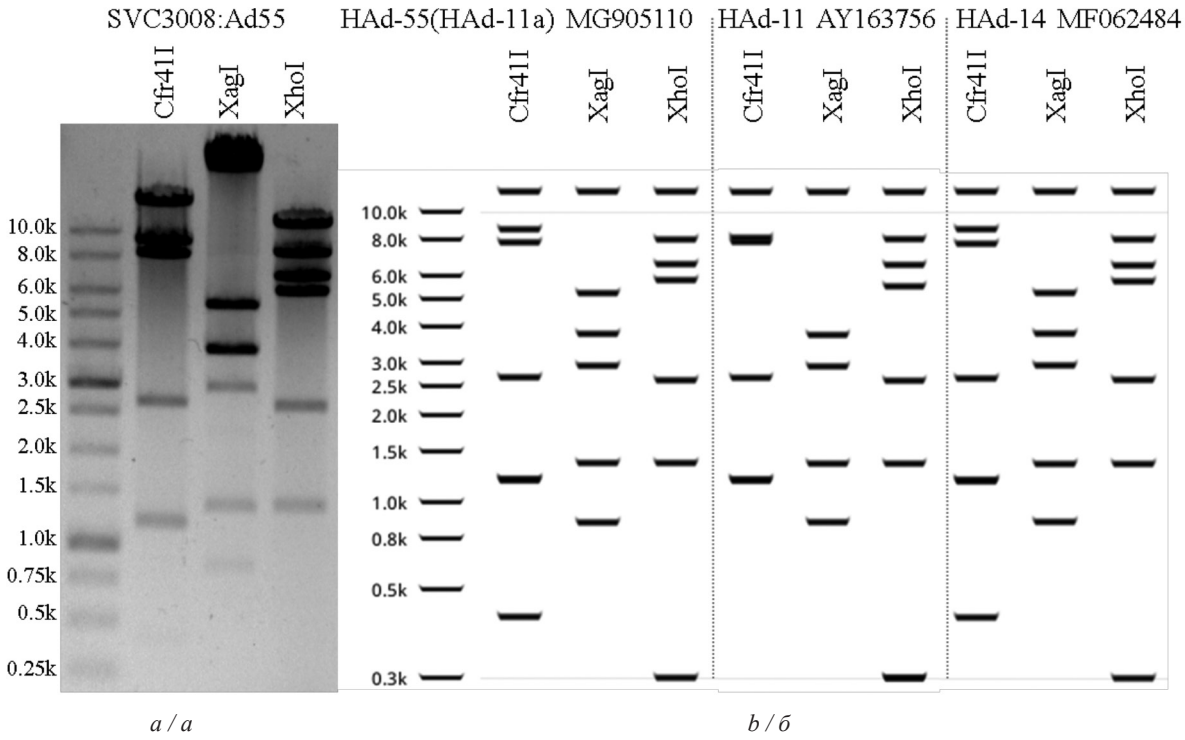


Fig. 1. Restriction fragment length polymorphisms (RFLPs) using Cfr41I, XagI, and XhoI restriction enzymes.
a – DNA of the SCV3008 isolate *in vitro*; *b* – DNA of the HAd-55, HAd-11 and HAd-14 strains *in silico.*
Рис. 1. Полиморфизм длин рестрикционных фрагментов, полученных с рестриктазами Cfr41I, XagI и XhoI.
а – для ДНК изолята SCV3008:Ad55 *in vitro*; *б* – для ДНК штаммов HAd-55, HAd-11 и HAd-14 *in silico*.

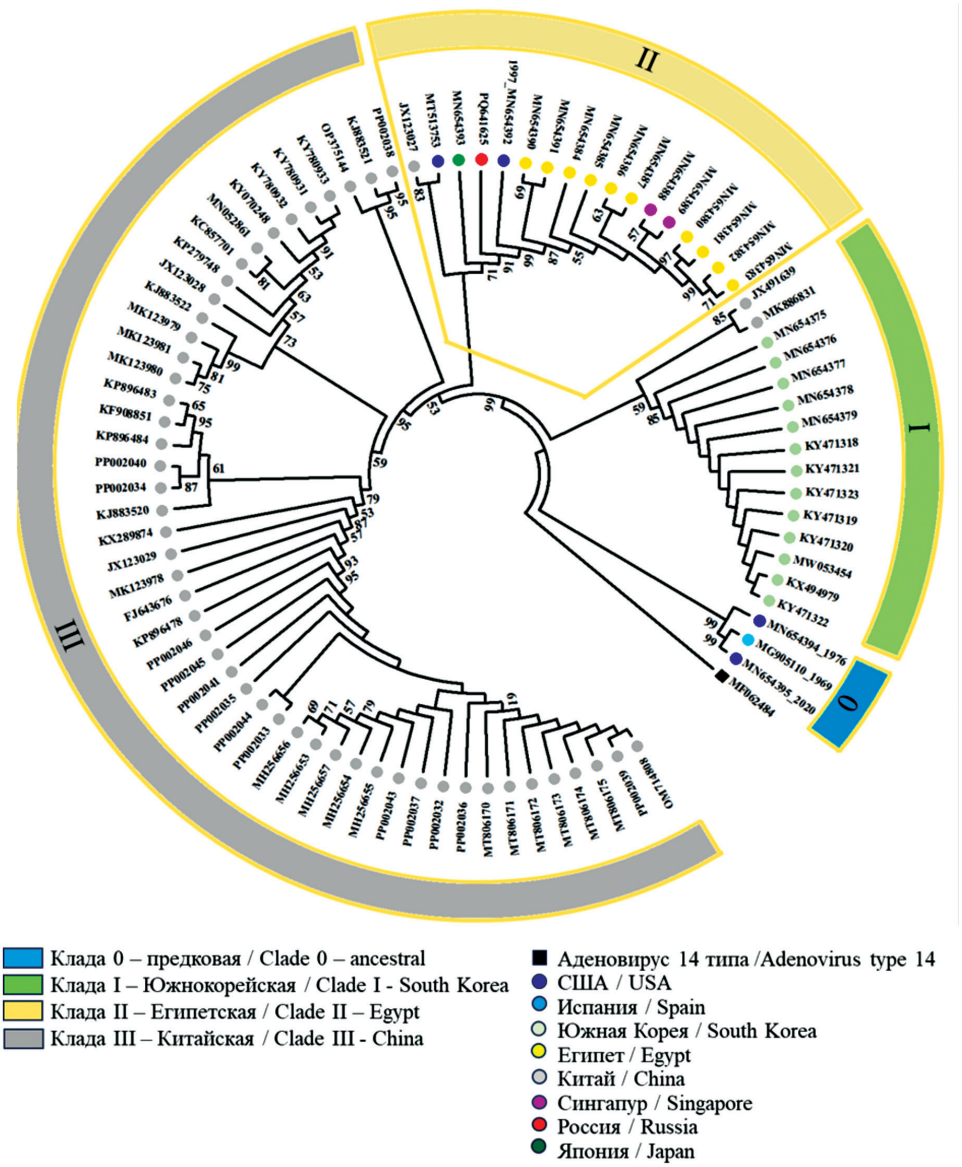


Fig. 2. Neighbor-joining phylogenetic tree constructed based on the complete genomes of 83 HAd-55 isolates presented in Table 1, and the genome of the SCV3008:Ad55 isolate (PQ641625).

Clades 0–III are characterized in the legend. MF062484 – HAd-14 isolate, represents an outgroup.

Рис. 2. Филогенетическое древо Neighbor-joining, построенное на основе полных геномов 83 изолятов HAd-55, представленных в табл. 1, и генома изолята SCV3008:Ad55 (PQ641625).

Клады 0–III охарактеризованы в легенде. MF062484 – изолят HAd-14, представляет внешнюю группу.

and HAdV-14 (MF062484). The ANI value between HAdV-55 and HAdV-14 was 98.7478–98.9411, and between the genomes of HAdV-55 it was 99.6546–100.000.

The phylogenetic analysis included HAdV-55 isolates collected in 8 countries from 1969 to 2022 (Table 1). The phylogenetic tree is illustrated in **Fig. 2**, which shows that the genomes formed 4 clades. The ancestral clade "0" included the earliest isolates MG905110 (Spain, 1969), MN654394 (USA, 1976), and the isolate MN654395 (USA, 2020). Clade I was formed by 13 isolates from South Korea and two isolates from China (2011 and 2015). Clade II, which was primarily composed of isolates from Egypt (12 isolates), was the most diverse in terms of country representation. It included isolates from Singapore (MN654388 and MN654389, 2005), Japan (MN654393, 2012), the USA (MN654392, 1997; MT513753, 2006), China (JX123027, 2010), and the isolate SCV3008:Ad55 identified by us. The most numerous clade III was formed by isolates from China from 2006 to 2021.

In clade II, the isolate closest to SCV3008:Ad55 in terms of ANI (99.9396) was the isolate from Japan (MN654393). Differences between the genomes SCV3008:Ad55 and MN654393 were identified both in the untranslated regions of the genome and in the genes of structural and non-structural proteins (**Table 2**). The

Table 2. Characterization of substitutions in the genome of isolate SVC308-Ad55

Таблица 2. Характеристика замен в геноме изолята SVC308:Ad55

Name of the region of the genome/CDS Название области генома/CDS	Substitution in the **SVC308:Ad55** genome relative to the WPAFB415 Замена в геноме **SVC308:Ad55** относительно генома WPAFB415	Mutation frequency Встречаемость мутации	Substitutions in amino acid sequence Замены в последовательности белка
Untranslated regions Нетранслируемые области	C134**T****	Clade Egypt*	
	A445**G**	SVC308:Ad55	
	T3437**C**	SVC308:Ad55	
	A3924**G**	SVC308:Ad55	
	G34619**T*****	SVC308:Ad55	
pIX 14.2 kDa / 14,2 кДа	C3536**T**	SVC308:Ad55	
pIVa2 50.9 kDa / 50,9 кДа	T4656**C**	WPAFB415	
128,9 кДа ДНК-полимераза 128.9 kDa DNA polymerase	C6707**T**	SVC308:Ad55	
	T6764**A**	WPAFB415	Lys→Asp
pTP 73.4 kDa / 73,4 кДа	G8779**A**	SVC308:Ad55	
	C8815**T**	Clade Egypt*	
L1 52/55K 43,9 kDa / 43,9 кДа	C11734**T**	SVC308:Ad55	
L1 pIIIa 65.6 kDa / 65,6 кДа	G13349**A**	Clade Egypt*	
L2 62,5 kDa penton protein / пентон 62,5 кДа	T13787**A**	SVC308:Ad55	Thr→Ala
	G14203**A**	SVC308:Ad55	
L2 pV 40.1 kDa / 40,1 кДа	T16315**C**	WPAFB415	Glu→Leu
	G16530**C**	WPAFB415	
58.3 kDa DNA-binding protein E2A 58,3 кДа ДНК-связывающий белок	G22776**A**	SVC308:Ad55	
L4 22K 21.6 kDa / 21,6 кДа	C26083**T**	Clade Egypt*	His→Tyr
L4 pVIII 25 kDa / 25 кДа	A26918**G**	WPAFB415	
E3 18.5 kDa / 18,5 kDa	T28096**G**	SVC308:Ad55	

Note. * – except for MT513753, MN654393, JX123027; ** – the left ITR region is found in only 65 of the 85 genomes; *** – the region of the genome in front of the right ITR is present in only 75 out of 85 genomes.

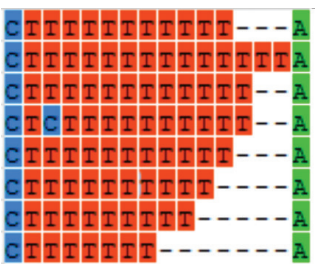
Примечание. * – кроме MT513753, MN654393, JX123027; ** – область левого ITR есть только в 65 геномах из 85; *** – область генома перед правым ITR присутствует только в 75 геномах из 85.

identified substitutions were compared with the sequences of other genomes in the sample. Note that the comparison of the ITR regions and the nearest ones was not possible for all genomes. Of the identified substitutions, 4 were characteristic of most isolates of clade II, 4 were unique to the genome of the Japanese isolate, and 12 substitutions distinguished the SCV3008:Ad55 isolate.

The substitutions in 4 reading frames were non-synonymous. The mutation in the peptide (Thr29Ala) was unique to the isolate SCV3008:Ad55. Changes in the DNA polymerase (Asp566Lys) and in the pV protein (Leu105Glu) distinguished the Japanese isolate MN654393. The mutation in the L4 22K protein (His162Tyr) was found in 14 isolates of clade II, including SCV3008:Ad55 (Table 2).

In the analysis of genomes, we noticed the heterogeneity in the sizes of poly-A/poly-T sequences in intergenic regions (**Table 3**). The sizes of regions 2–6, marked in the SCV3008:Ad55 genome, were characteristic of many genomes in the HAdV-55 sample. Region 1 with the A6G substitution was unique to SCV3008:Ad55. Homopolymer sequences in adenovirus genomes, also known as microsatellites, drew the attention of researchers during the investigation of adenovirus infection outbreaks with fatal outcomes in U.S. military cohorts in 2006–2007. Polymorphism of microsatellite loci lengths became a high-resolution marker for attributing HAdV-14 to a single outbreak [18]. A comparison of microsatellite loci in the isolates of clade II «Egypt» was conducted, which included 17 isolates from different continents. The data in

Table 3. Regions of repeats in the genomes of a sample of adenoviruses belonging to genotype 55
Таблица 3. Области повторов в геномах выборки аденовирусов человека 55-го типа

N	The position according to PQ641625 genome / Neighboring ORS Положение по геному PQ641625 / Соседние ОРС	Isolate Изолят	The number of nucleotides in the repeat Число нуклеотидов в повторе	Number of isolates Количество изолятов
1	3918–3933 bp / pIX; pIVa2	MF062484/China/2010*		1
		OP375144/China/2021		3
		MW053454/China/2023		1
		PQ641625/Russia/2022		1
		MN654393/Japan/2012		1
		MN654378/S.Korea/2009		24
		MN654392/USA/1997		5
		MN654394/USA/1976		1
		FJ643676/China/2011		48
2	10651–10664 bp / pTP; L1	MF062484/China/2010*		
		MN654395/USA/2020		1
		MW053454/China/2023		3
		KY471322/S.Korea/2017		9
		PP002032/China/2018		21
		PQ641625/Russia/2022		7
		MN654394/USA/1976		37
		MK123980/China/2013		6
		KP896484/China/2013		1
3	13620–13630 bp/L1 pIIIa; L2 penton [polyA_signal_sequence (aaataaa) 13627–13633 bp]	MF062484/China/2010*		1
		PP002034/China/2018		1
		MN654388/Singapore/2005		16
		PQ641625/Russia/2022		66
		PP002040/China/2018		1
4a	17323–17334 bp / L2 pX; L3 pVI	MF062484/China/2010*		
		MK123978/China/2018		1
		PQ641625/Russia/2022		51
		KY070248/China/2016		20
		MN654394/USA/1976		12
		KP896484/China/2013		1
4b	17341–17352 bp / L2 pX; L3 pVI [polyA_signal_sequence (aataaa) 17339–17344 bp]	MF062484/China/2010*		
		KX494979/S.Korea/2016		5
		PQ641625/Russia/2022		75
		KH289874/China/2015		5
5	29474–29486 bp / E3 20.2 kDa; E3 10.3 kDa	MF062484/China/2010*		
		MT513753/USA/2006		1
		MK123981/China/2013		3
		OM714808/China/2020		1
		PQ641625/Russia/2022		17
		KP896483/China/2013		37
		JX123029/China/2012		25
		KP896484/China/2013		1
6	34006 – 34016 bp / E4 ORF2; E4 ORF1	MF062484/China/2010*		1
		MT513753/USA/2006		3
		PQ641625/Russia/2022		28
		JX123029/China/2012		53

Note. * – the ancestral genome of human adenovirus 14.

Примечание. * – предковый геном Human adenovirus 14.

Таблица 4. Размер локусов микросателлитов в геномах изолятов клады II «Egypt»
Table 4. Size of microsatellite loci in the genomes of clade II «Egypt» isolates

Локус Locus	Изолят Isolate	Размер гомополимера (нт) Homopolymer size (nt)	Локус Locus	Изолят Isolate	Размер гомополимера (нт) Homopolymer size (nt)
1	Большинство* / Most	A (13)	4a, 4b	Большинство / Most	A (10); A (10)
	MN654380 (Egypt 2000)	A (12)		JX123027 (China 2010)	A (10); A (11)
	MN654392 (USA 1997)	A (12)		MN654392 (USA 1997)	A (9); A (10)
	MN654393 (Japan 2012)	A (14)	5	Большинство / Most	T (9)
	PQ641625 (Russia 2022)	A (13) G (1)		MN654393 (Japan 2012)	T (11)
2	Большинство / Most	T (11)		PQ641625 (Russia 2022)	T (11)
	MN654393 (Japan 2012)	T (12)		JX123027 (China 2010)	T (10)
	PQ641625 (Russia 2022)	T (12)		MT513753 (USA 2006)	T (14)
	JX123027 (China 2010)	T (12)	6	Большинство / Most	A (8)
3	Большинство / Most	A (10)		MN654393 (Japan 2012)	A (10)
	MN654386 (Egypt 2007)	A (11)		PQ641625 (Russia 2022)	A (10)
	MN654387 (Egypt 2009)	A (11)		MT513753 (USA 2006)	A (11)
	MN654388 (Singapore 2005)	A (11)			
	MN654389 (Singapore 2005)	A (11)			

Примечание. * – в кладе II «Egypt» 17 изолятов.

Note. * – Clade II «Egypt» contains 17 isolates.

Table 4 indicate that most isolates of clade II were similar in microsatellite size across all 6 loci. The maximum number of loci (4) distinguished the genomes of isolates from Japan (MN654393) and Russia (SCV3008:Ad55), the genome of the single isolate from China in clade II (JX123027) differed by 3 loci, the isolates from the USA (MN654392, 1997; MT513753, 2006) differed by 2 different loci, and the isolates from Singapore (MN654388 and MN654389) differed by 1 locus each. Of the 10 Egyptian isolates in clade II, three had one locus difference each. Thus, with the high conservatism of HAdV-55 genomes, microsatellite loci indeed allow for the differentiation of virus genomes within a single clade.

Discussion

For the first time, the presented study describes the genome of the HAdV-55 SCV3008:Ad55 strain isolated in the territory of the Russian Federation. It should be noted that previous molecular-epidemiological genomic studies of adenoviruses in the Russian Federation are rare and focused on the study of *M. caesari* HAdV, pathogens of respiratory infections in children [19]. The collection of comparative information for genomic studies is hindered by the low level of implementation of genotyping methods in the laboratory diagnosis of adenovirus infection.

In Russia, the molecular-genetic approach, approved since 2010, is used for epidemiological monitoring for adenovirus infection and identification of the pathogen up to the family Adenoviridae at the Reference Center for Influenza and ARVI Diagnosis based at the A.A. Smorodintsev Research Institute of Influenza, at the Center for Ecology and Epidemiology of Influenza at the N.F. Gamaleya National Research Center for Epidemiology and Microbiology, and at the reference bases of Rospotrebnadzor. Adenovirus infections in children are under special control and are also subject to molecular diagnostics according to clinical guidelines[2]. However, HAdV genotyping is not included in the list of laboratory diagnostic methods.

ECDC (European Centre for Disease Prevention and Control) does not conduct routine surveillance of adenovirus infections and only records outbreaks of the disease, whereas the CDC (Centers for Disease Control and Prevention, USA) has developed guidelines for identifying HAdV based on nucleic acid amplification and has created the National Adenovirus Type Reporting System (NATRS). According to NATRS data from 2017 to 2023, HAdV 6 genotypes were the most common in the USA, among which HAdV-7 and HAdV-14 of the *M. blackbeardi* species accounted for 13.4% and 7.8%, respectively (https://www.cdc.gov/adenovirus/hcp/outbreaks/index.html). The Japanese National Infectious Disease Epidemiological Surveillance System also conducts adenovirus genotyping, noting among the predominant *M. blackbeardi* HAdV-3, 7, 11, 34, 35, and

[2]Clinical guidelines (treatment protocol) for providing medical care to children with adenoviral infection; 2013. Available at: http://niidi.ru/dotAsset/69f7f879-9765-4634-a621-8792acf587b7.pdf

among the minor ones 14, 16, 55, 66, 68, 79 [20]. The CDC of China monitors influenza and ARVI, but does not publish reports on virus genotyping in the public domain [21]. Thus, among national surveillance systems, only Japan's epidemiological surveillance system monitors HAdV-55.

Analysis of scientific publications from 2012 to 2025, available on PubMed, showed that out of 48 articles mentioning HAdV-55 in their keywords, 39 (81%) were published by researchers from China, 7 from South Korea, and one each from the USA and Senegal. This ratio of publications confirms the endemicity of HAdV-55 in China and South Korea. It should be noted that among the publications from South Korea, only two present a study of HAdV-55 infections among the civilian population, while the others describe outbreaks of ARVI caused by HAdV-55 among military personnel [22]. The topic of HAdV-55 infections among military personnel is continued by a publication from the USA [23], dedicated to the analysis of the MW053454 virus isolate, which was isolated from an American serviceman who was in South Korea in 2019. The MW053454 isolate differed from the South Korean isolate KX494979 from 2016 by one synonymous substitution. In the current study, both isolates were placed in clade I «South Korea». In Senegal, from 2012 to 2015, *M. blackbeardi* HAdV was identified in 9 cases of patients with ARVI, among which HAdV-7, HAdV-55 and HAdV-11 were noted [24]. The presented data indicate that HAdV genotyping is gradually being integrated into laboratory practice.

Considering the above, in order to conduct a comparative study of the genome of the isolate SCV3008:Ad55, GenBank data was used, collecting a sample of 83 isolates from 1969 to 2022 from 7 countries. The analysis of the sample showed a high similarity of HAdV-55 genomes, reaching 99.7–100% on the ANI scale, which is consistent with data from other studies conducted on a smaller number of isolates [25]. At the same time, the phylogenetic analysis allowed for the division of the genomes in the sample into clades, indicating the presence of heterogeneity even with high homology. Clades I and III corresponded to the geographical origin of the isolates and showed an epidemiological connection both between the isolates from China and those from South Korea. Isolates from Egypt from 2000 to 2009, a country distant from areas endemic to HAdV-55, clustered with isolates from five countries, including China, indicating the spread of HAdV-55, facilitated by globalization processes. It should be noted that the isolates in cluster II predominantly came from the civilian population. The exceptions were the isolates from Singapore and Japan, obtained from samples of military personnel who fell ill with ARVI [25].

Comparative genomic analysis revealed differences in the SVC3008:Ad55 isolate, specifically 12 point mutations distributed throughout the genome, of which a non-synonymous substitution occurred in the reading frame of the 62.5 kDa penton L2, leading to a T29A substitution at the N-terminus of the protein sequence. Since the substitution is conservative, it does not affect the amphipathic properties of the N-terminal helix of the protein or the capability of the PPRY motif (42–45 a.a.) to interact with the WW domains of cellular ubiquitin ligases, which facilitates the virus's entry into the eukaryotic cell, determining its infectivity [26].

Additional information about the diversity of closely related genomes of the clade II isolates was provided by the analysis of microsatellite length polymorphism (homopolymers) at 6 loci in the untranslated regions. Out of 17 isolates of the clade, 10 had differences in at least one locus. The isolates from Japan and Russia differed from the other isolates of the clade by 4 microsatellite loci. This approach even allowed for the differentiation of isolates from Egypt within two regions: Alexandria (2000–2002) and Cairo (2005–2009).

Conclusion

Comparative genomic study of HAdV-55 isolates, which emerged as a result of the recombination of HAdV-14 and HAdV-11, showed genome stability since 1969 and a slow accumulation of mutations in both coding and non-coding regions, allowing the identification of unique substitutions in the new SVC3008:Ad55 isolate. The obtained genomic information laid the foundation for the development of diagnostic kits and further monitoring for HAdV-55, which causes infections complicated by bronchopneumonia. At the same time, since adenoviruses are subject to recombinational variability and there are multiple recombination hotspots (genes of the penton, hexon, fiber, E1, E3 and E4) [27], whole-genome sequencing is particularly effective in monitoring and molecular epidemiological analysis of adenovirus pathogens.

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