Genome Sequence of a Cynomolgus Macaque Adenovirus (CynAdV-1) Isolate from a Primate Colony in the United Kingdom

AMERICAN SOCIETY FOR MICROBIOLOGY | genomeAnnouncements

Genome Sequence of a Cynomolgus Macaque Adenovirus (CynAdV-1) Isolate from a Primate Colony in the United Kingdom

Zhiwei Zeng,[a] Jing Zhang,[a] Shuping Jing,[a] Zetao Cheng,[a] Silvia Bofill-Mas,[b] Carlos Maluquer de Motes,[b]* Ayalkibet Hundesa,[b] Rosina Girones,[b] Donald Seto,[c] Qiwei Zhang[a,d]

Biosafety Level-3 Laboratory, School of Public Health, Southern Medical University (Guangdong Provincial Key Laboratory of Tropical Disease Research), Guangzhou, Guangdong, China[a]; Section of Microbiology, Virology and Biotechnology, Department of Genetics, Microbiology and Statistics, University of Barcelona, Barcelona, Spain[b]; Bioinformatics and Computational Biology Program, School of Systems Biology, George Mason University, Manassas, Virginia, USA[c]; Department of Ophthalmology, Howe Laboratory, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts, USA[d]

* Present address: Carlos Maluquer de Motes, Department of Microbial Sciences, University of Surrey, Guilford, United Kingdom.

The genome sequence of a simian adenovirus from a cynomolgus macaque, denoted CynAdV-1, is presented here. Phylogenetic analysis supports CynAdV-1 in an independent clade, comprising a new simian adenovirus (SAdV) species. These genome data are critical for understanding the evolution and relationships of primate adenoviruses, including zoonosis and emergent human pathogens.

Received 1 September 2016 **Accepted** 12 September 2016 **Published** 3 November 2016

Citation Zeng Z, Zhang J, Jing S, Cheng Z, Bofill-Mas S, Maluquer de Motes C, Hundesa A, Girones R, Seto D, Zhang Q. 2016. Genome sequence of a cynomolgus macaque adenovirus (CynAdV-1) isolate from a primate colony in the United Kingdom. Genome Announc 4(6):e01193-16. doi:10.1128/genomeA.01193-16.

Address correspondence to Donald Seto, dseto@gmu.edu, or Qiwei Zhang, zhang.qiwei@yahoo.com.

Adenoviruses infect a broad range of vertebrate hosts, including humans and nonhuman primates (1). To date, at least 69 different human adenoviruses (HAdVs) and 25 simian adenoviruses (SAdVs) have been described and grouped into eight human (A to G) and one simian (A) species (1, 2). Additionally, adenoviruses are reported in cross-species zoonotic transmissions, for example, between nonhuman primates and human hosts (3–7). In one seminal example, HAdV-4, a major human respiratory pathogen and one of the original identified and characterized human respiratory adenoviral pathogens, has been characterized as a chimpanzee virus that has transferred hosts stably through zoonosis (6–9). As human pathogens, HAdVs can produce latent and asymptomatic infections as well as cause mild to severe disease, including death. They can affect the respiratory, ocular, gastrointestinal, metabolic, and urogenital systems (10–12). Over the last decade, HAdVs, and especially SAdVs, have become important tools for improving human health as gene delivery vectors for gene therapy and for vaccine development (13, 14). Given the possibility of preexisting immunity against HAdVs in humans, SAdVs are a valuable alternative, as they are presumably not found in humans (15–17).

SAdVs have been isolated from apes, including chimpanzees (18, 19), and monkeys, including macaques and baboons (4, 20). Cross-species zoonotic transmissions have been reported, with both hosts retaining antigenic profiles of the event (3, 4). These zoonotic events are important, as genome recombination is documented among HAdVs as a pathway of generating novel human pathogens that cause acute respiratory and epidemic keratoconjunctivitis diseases (21–23); therefore, genome recombination with SAdVs may be another pathway for the genesis of emergent human pathogens (5). In this context, the further and additional characterization of SAdVs from apes and monkeys is of critical importance for understanding SAdVs as human pathogens and as vectors in the development of gene therapy and vaccine vectors.

Cynomolgus adenovirus 1/UK/UK-1/2004 was isolated from a colony of cynomolgus macaques (*Macaca fascicularis*) (20). Its genome (35,555 nucleotides) was sequenced using an Ion Torrent on the Personal Genome Machine and assembled with CLC Genomics Workbench 7 (CLC bio; Aarhus, Denmark). It yielded 12.8 Mb filtered reads with an average read length of 180 bp, 110× coverage, and an N_{50} of 1,226 bp. This was supplemented with the Sanger chemistry method to fill gaps and ambiguous sequences. Initial gene analyses by Maluquer de Motes et al. (20) and preliminary whole-genome analysis indicate that CynAdV-1 is in a unique subclade, branching with SAdV-6 and -3, and that all three are contained in a larger clade that includes HAdV species A, F, and G. Discussions of the concept of HAdV and SAdV "species" are ongoing; this CynAdV-1 genome sequence will add to the discussions and understanding of the relationships between HAdVs and SAdVs, including a combined and integrated tree with proposed "primate AdV" species, as the HAdVs and SAdVs are phylogenetically close and all species branch from one common phylogenetic tree.

Accession number(s). Genome data for cynomolgus adenovirus 1/UK/UK-1/2004 are available in the GenBank database under the accession number KT013209.

ACKNOWLEDGMENTS

Portions of this manuscript were completed at the Department of Ophthalmology, Howe Laboratory, Massachusetts Eye and Ear Infirmary, Harvard Medical School (Boston, Massachusetts, USA) as Q.Z. was funded by the China Scholarship Council (CSC No. 201508440056) as a Visiting Scholar (2015-2016); he thanks Professor James Chodosh for providing a stimulating intellectual environment.

FUNDING INFORMATION

This work, including the efforts of Qiwei Zhang, was funded by Excellent Young Teacher Training Plan of Guangdong Province (Yq2013039). This work, including the efforts of Qiwei Zhang, was funded by Young Top-notch Talents of the Guangdong Province Special Support Program (2014). This work, including the efforts of Donald Seto, was funded by The Office of the Vice President for Research at George Mason University (Summer Research Grant). This work, including the efforts of Qiwei Zhang, was funded by China Scholarship Council (CSC) (201508440056).

REFERENCES

1. **Harrach B, Benkö M, Both GW, Brown M, Davison AJ, Echavarria M, Hess M, Jones MS, Kajon A, Lehmkuhl HD, Mautner V, Mittal SK, Wadell G.** 2011. Family *Adenoviridae*, p 125–141. *In* King AMQ, Adams MJ, Carstens EB, Lefkowitz EJ (ed), Virus taxonomy: classification and nomenclature of viruses. Ninth Report of the International Committee on Taxonomy of Viruses. Elsevier, San Diego, CA.
2. **Singh G, Zhou X, Lee JY, Yousuf MA, Ramke M, Ismail AM, Lee JS, Robinson CM, Seto D, Dyer DW, Jones MS, Rajaiya J, Chodosh J.** 2015. Recombination of the epsilon determinant and corneal tropism: human adenovirus species D types 15, 29, 56, and 69. Virology **485:**452–459. http://dx.doi.org/10.1016/j.virol.2015.08.018.
3. **Chen EC, Yagi S, Kelly KR, Mendoza SP, Tarara RP, Canfield DR, Maninger N, Rosenthal A, Spinner A, Bales KL, Schnurr DP, Lerche NW, Chiu CY.** 2011. Cross-species transmission of a novel adenovirus associated with a fulminant pneumonia outbreak in a new world monkey colony. PLoS Pathog **7:**e1002155. http://dx.doi.org/10.1371/journal.ppat.1002155.
4. **Chiu CY, Yagi S, Lu X, Yu G, Chen EC, Liu M, Dick EJ, Jr, Carey KD, Erdman DD, Leland MM, Patterson JL.** 2013. A novel adenovirus species associated with an acute respiratory outbreak in a baboon colony and evidence of coincident human infection. mBio **4:**e00084-13. http://dx.doi.org/10.1128/mBio.00084-13.
5. **Dehghan S, Seto J, Jones MS, Dyer DW, Chodosh J, Seto D.** 2013. Simian adenovirus type 35 has a recombinant genome comprising human and simian adenovirus sequences, which predicts its potential emergence as a human respiratory pathogen. Virology **447:**265–273. http://dx.doi.org/10.1016/j.virol.2013.09.009.
6. **Dehghan S, Seto J, Liu EB, Walsh MP, Dyer DW, Chodosh J, Seto D.** 2013. Computational analysis of four human adenovirus type 4 genomes reveals molecular evolution through two interspecies recombination events. Virology **443:**197–207. http://dx.doi.org/10.1016/j.virol.2013.05.014.
7. **Purkayastha A, Ditty SE, Su J, McGraw J, Hadfield TL, Tibbetts C, Seto D.** 2005. Genomic and bioinformatics analysis of HAdV-4, a human adenovirus causing acute respiratory disease: implications for gene therapy and vaccine vector development. J Virol **79:**2559–2572. http://dx.doi.org/10.1128/JVI.79.4.2559-2572.2005.
8. **Rowe WP, Huebner RJ, Gilmore LK, Parrott RH, Ward TG.** 1953. Isolation of a cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture. Proc Soc Exp Biol Med **84:**570–573. http://dx.doi.org/10.3181/00379727-84-20714.
9. **Hilleman MR, Werner JH.** 1954. Recovery of new agent from patients with acute respiratory illness. Proc Soc Exp Biol Med **85:**183–188.
10. **Echavarría M.** 2008. Adenoviruses in immunocompromised hosts. Clin Microbiol Rev **21:**704–715. http://dx.doi.org/10.1128/CMR.00052-07.
11. **Lion T.** 2014. Adenovirus infections in immunocompetent and immunocompromised patients. Clin Microbiol Rev **27:**441–462. http://dx.doi.org/10.1128/CMR.00116-13.
12. **Garnett CT, Talekar G, Mahr JA, Huang W, Zhang Y, Ornelles DA, Gooding LR.** 2009. Latent species C adenoviruses in human tonsil tissues. J Virol **83:**2417–2428. http://dx.doi.org/10.1128/JVI.02392-08.
13. **Thacker EE, Timares L, Matthews QL.** 2009. Strategies to overcome host immunity to adenovirus vectors in vaccine development. Expert Rev Vaccines **8:**761–777. http://dx.doi.org/10.1586/erv.09.29.
14. **Zhang Q, Seto D.** 2015. Chimpanzee adenovirus vector Ebola vaccine—preliminary report. N Engl J Med **373:**775–776. http://dx.doi.org/10.1056/NEJMc1505499.
15. **Calcedo R, Vandenberghe LH, Roy S, Somanathan S, Wang L, Wilson JM.** 2009. Host immune responses to chronic adenovirus infections in human and nonhuman primates. J Virol **83:**2623–2631. http://dx.doi.org/10.1128/JVI.02160-08.
16. **Roy S, Gao G, Lu Y, Zhou X, Lock M, Calcedo R, Wilson JM.** 2004. Characterization of a family of chimpanzee adenoviruses and development of molecular clones for gene transfer vectors. Hum Gene Ther **15:**519–530. http://dx.doi.org/10.1089/10430340460745838.
17. **Roy S, Vandenberghe LH, Kryazhimskiy S, Grant R, Calcedo R, Yuan X, Keough M, Sandhu A, Wang Q, Medina-Jaszek CA, Plotkin JB, Wilson JM.** 2009. Isolation and characterization of adenoviruses persistently shed from the gastrointestinal tract of non-human primates. PLoS Pathog **5:**e1000503. http://dx.doi.org/10.1371/journal.ppat.1000503.
18. **Rowe WP, Hartley JW, Huebner RJ.** 1956. Additional serotypes of the APC virus group. Exp Biol Med **91:**260–262. http://dx.doi.org/10.3181/00379727-91-22231.
19. **Basnight M, Jr, Rogers NG, Gibbs CJ, Jr, Gajdusek DC.** 1971. Characterization of four new adenovirus serotypes isolated from chimpanzee tissue explants. Am J Epidemiol **94:**166–171.
20. **Maluquer de Motes C, Hundesa A, Almeida FC, Bofill-Mas S, Girones R.** 2011. Isolation of a novel monkey adenovirus reveals a new phylogenetic clade in the evolutionary history of simian adenoviruses. Virol J **8:**125. http://dx.doi.org/10.1186/1743-422X-8-125.
21. **Robinson CM, Singh G, Henquell C, Walsh MP, Peigue-Lafeuille H, Seto D, Jones MS, Dyer DW, Chodosh J.** 2011. Computational analysis and identification of an emergent human adenovirus pathogen implicated in a respiratory fatality. Virology **409:**141–147. http://dx.doi.org/10.1016/j.virol.2010.10.020.
22. **Walsh MP, Chintakuntlawar A, Robinson CM, Madisch I, Harrach B, Hudson NR, Schnurr D, Heim A, Chodosh J, Seto D, Jones MS.** 2009. Evidence of molecular evolution driven by recombination events influencing tropism in a novel human adenovirus that causes epidemic keratoconjunctivitis. PLoS One **4:**e5635. http://dx.doi.org/10.1371/journal.pone.0005635.
23. **Walsh MP, Seto J, Jones MS, Chodosh J, Xu W, Seto D.** 2010. Computational analysis identifies human adenovirus type 55 as a re-emergent acute respiratory disease pathogen. J Clin Microbiol **48:**991–993. http://dx.doi.org/10.1128/JCM.01694-09.