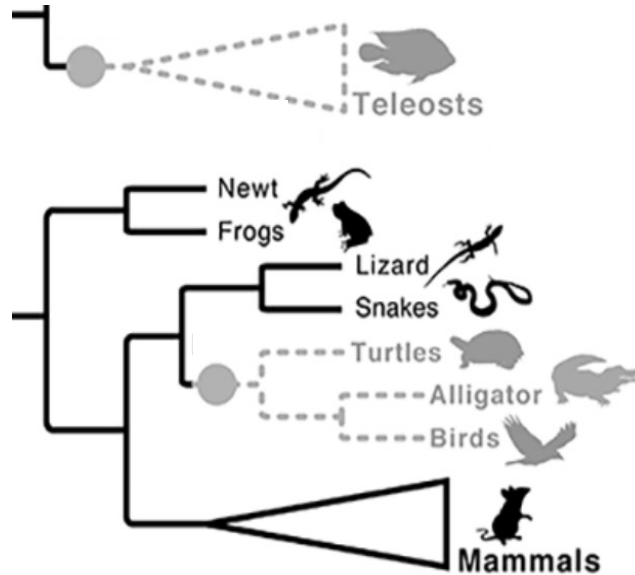


Update on Human Adenoviruses

Don Seto
School of Systems Biology
George Mason University

What are adenoviruses?

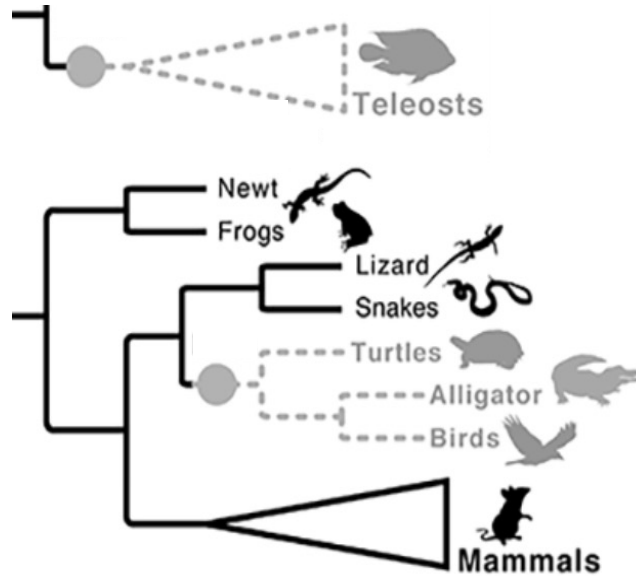


• *Adenoviridae*

- *Ichtadenovirus* (fish)
- *Testadenovirus* (reptile)
- *Siadenovirus* (bird, amphibian, reptile)
- *Aviadenovirus* (bird)
- *Atadenovirus* (bird, reptile, mammal)
- *Mastadenovirus* (mammal)
 - HAdV species, A-G
 - (Non-human) SAdV species, A-I
 - Other

- Non-enveloped, icosahedral, nucleocapsid virus containing a double-stranded linear DNA genome, *ca.* 24-46kb
- Hosted across (likely) all vertebrates

“Adenovirus lineage evolution”



• *Adenoviridae*

- *Ichtadenovirus* (fish)
- *Testadenovirus* (reptile)
- *Siadenovirus* (bird, amphibian, reptile)
- *Aviadenovirus* (bird)
- *Atadenovirus* (bird, reptile, mammal)
- *Mastadenovirus* (mammal)

- “PrAdV” {
- HAdV species, A-G
 - (Non-human) SAdV species, A-I
-ChAdV, GoAdV, MaAdV, BaAdV
 - Other

- Non-enveloped, icosahedral, nucleocapsid virus containing a double-stranded linear DNA genome; HAdV *ca.* 36kb

- **PrimateAdV**: Kang, J., et al. (2020). Genomics-based re-examination of the taxonomy and phylogeny of human and simian Mastadenoviruses: an evolving whole genomes approach... *Cladistics* 36:358

Human adenoviruses as pathogens



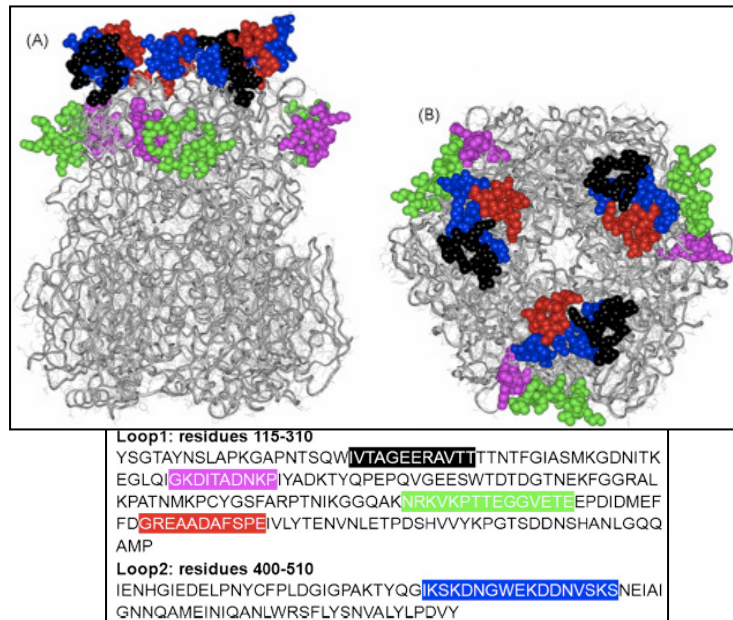
(Photo: BBC.Our.Secret.Universe.The.Hidden.Life.of.the.Cell.720p.HDTV)

- Human pathogen

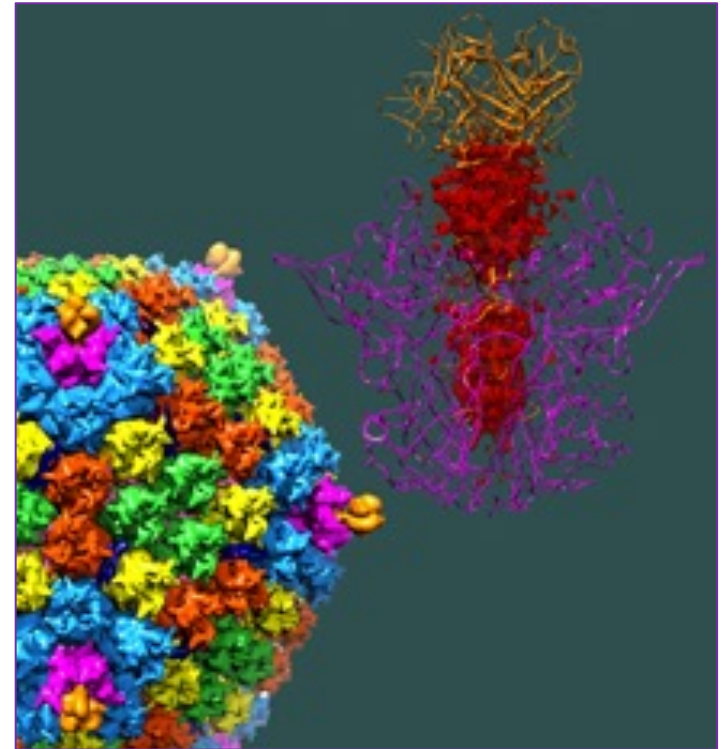
=> Symptoms range from none, mild to severe, latent; Highly contagious; Self-limiting

- Respiratory tract
- Ocular tract
- Gastrointestinal tract (hepatitis)
- Genitourinary tract
- Metabolic pathway(s) (obesity)
- Cardiac tissue (carditis)
- Central Nervous System (encephalitis)

Human adenoviruses, identification and characterization 1



(Yuan, X., *et al.* (2009). *Vaccine* 27:5103)



(Reddy, V.S., *et al.* (2010). *Sci* 329:1071)

- Serotyping *was* based on hexon and fiber epitopes (pre-2007)
 - Hexon- major capsid protein (83%) and epsilon epitope(s) (Serum neutralization)
 - Fiber- cell tropism and gamma epitope (Hemagglutination)

Identification and characterization of *novel* HAdV through genome sequencing

> [J Virol.](#) 2007 Jun;81(11):5978-84. doi: 10.1128/JVI.02650-06. Epub 2007 Mar 14.

New adenovirus species found in a patient presenting with gastroenteritis

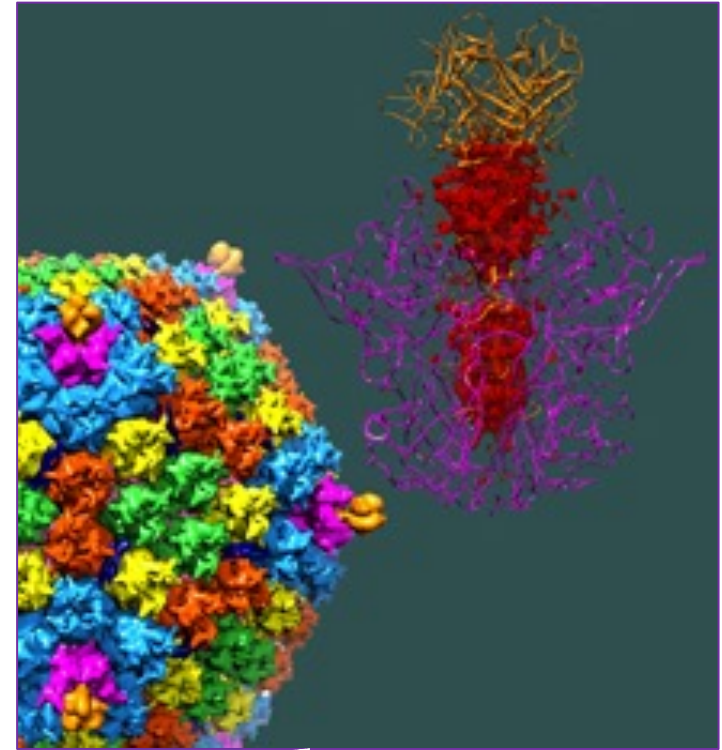
Morris Saffold Jones 2nd ¹, Balázs Harrach, Robert D Ganac, Mary M A Gozum, Wilfred P Dela Cruz, Brian Riedel, Chao Pan, Eric L Delwart, David P Schnurr

Affiliations + expand

PMID: 17360747 PMCID: [PMC1900323](#) DOI: [10.1128/JVI.02650-06](#)

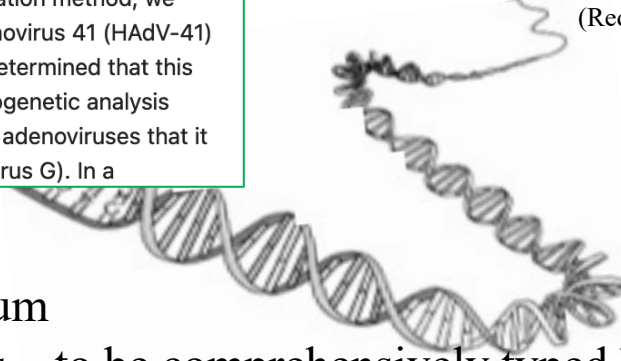
Abstract

An unidentified agent was cultured in primary monkey cells at the Los Angeles County Public Health Department from each of five stool specimens submitted from an outbreak of gastroenteritis. Electron microscopy and an adenovirus-specific monoclonal antibody confirmed this agent to be an adenovirus. Since viral titers were too low, complete serotyping was not possible. Using the DNase-sequence-independent viral nucleic acid amplification method, we identified several nucleotide sequences with a high homology to human adenovirus 41 (HAdV-41) and simian adenovirus 1 (SAdV-1). However, using anti-SAdV-1 sera, it was determined that this virus was serologically different than SAdV-1. Genomic sequencing and phylogenetic analysis confirmed that this new adenovirus was so divergent from the known human adenoviruses that it was not only a new type but also represented a new species (human adenovirus G). In a



(Reddy, V.S., *et al.* (2010). *Sci* 329:1071)

- Did not cross-react with SAdV-1 antiserum
- “..failed to replicate in high enough titers ...to be comprehensively typed by neutralization.”
- Not able to generate HAdV-52 antisera



HAdV lineage evolution

Using the Whole-Genome Sequence To Characterize and Name Human Adenoviruses

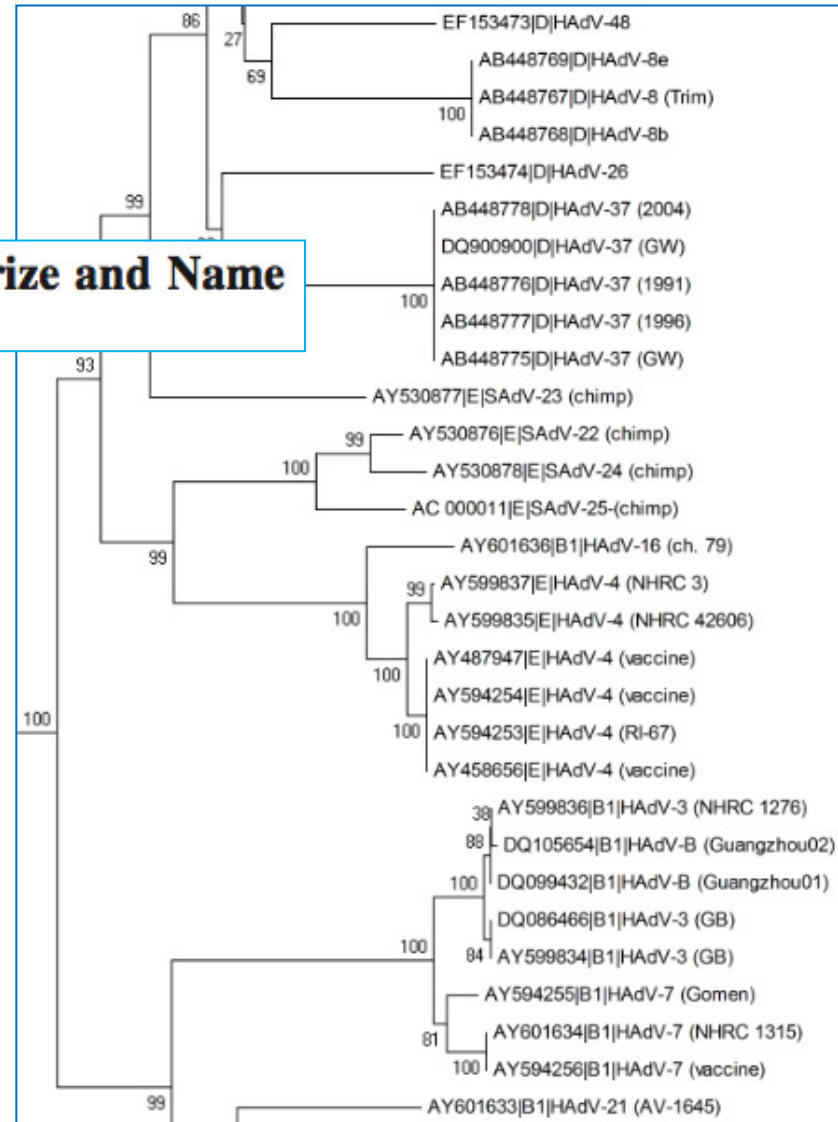
JOURNAL OF VIROLOGY, June 2011, p. 5701–5702

Donald Seto, James Chodosh, J Rodney Brister, Morris S Jones,
Members of the Adenovirus Research Community

We propose that human adenoviruses (HAdVs) be identified, characterized, and typed on the basis of complete genome sequence analyses rather than serological approaches. This

- Based on genome, penton base, hexon, and fiber
 - 100+ whole genomes in GenBank, 2011
 - Consistent with previous serology-based data*
 - Data/names compatible with databases, other viruses*

- Example- HAdV-53 is “Adenovirus D human/DEU/IAI-1/2005/53[P37H22F8]”



Paradigm shift: “Recombinants as novel types”

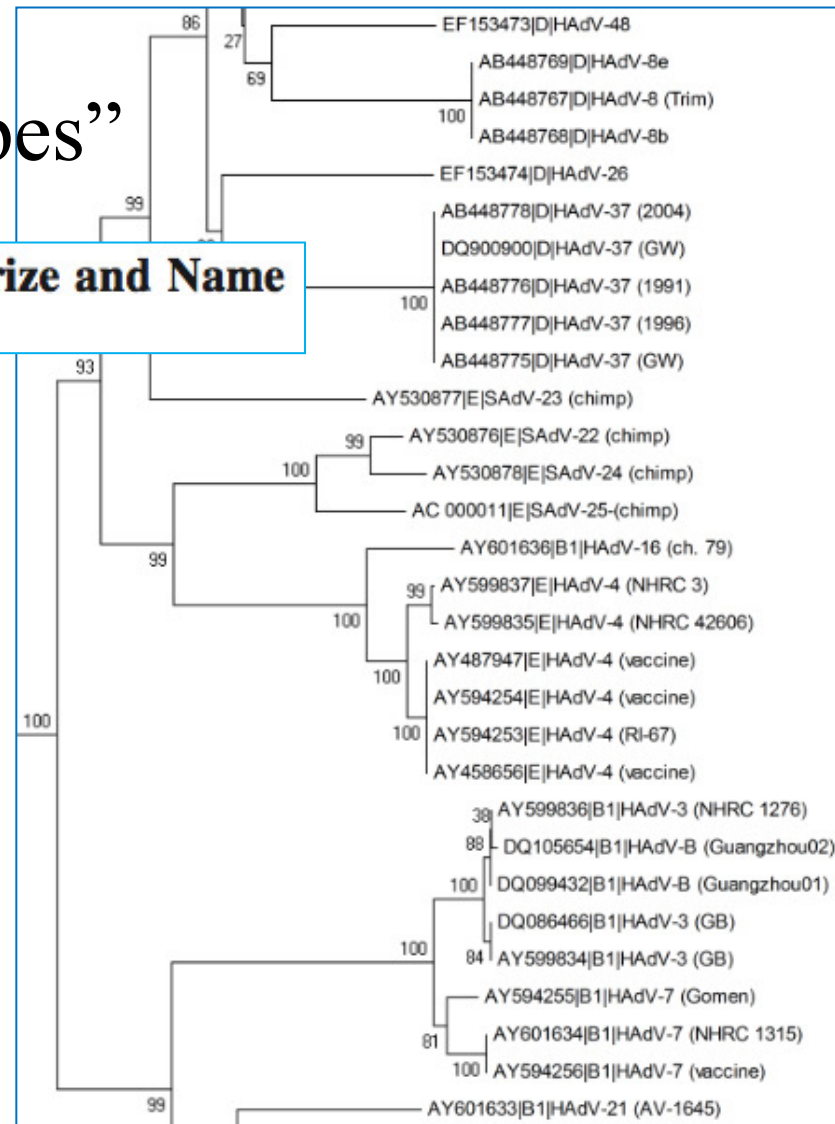
Using the Whole-Genome Sequence To Characterize and Name Human Adenoviruses

JOURNAL OF VIROLOGY, June 2011, p. 5701–5702

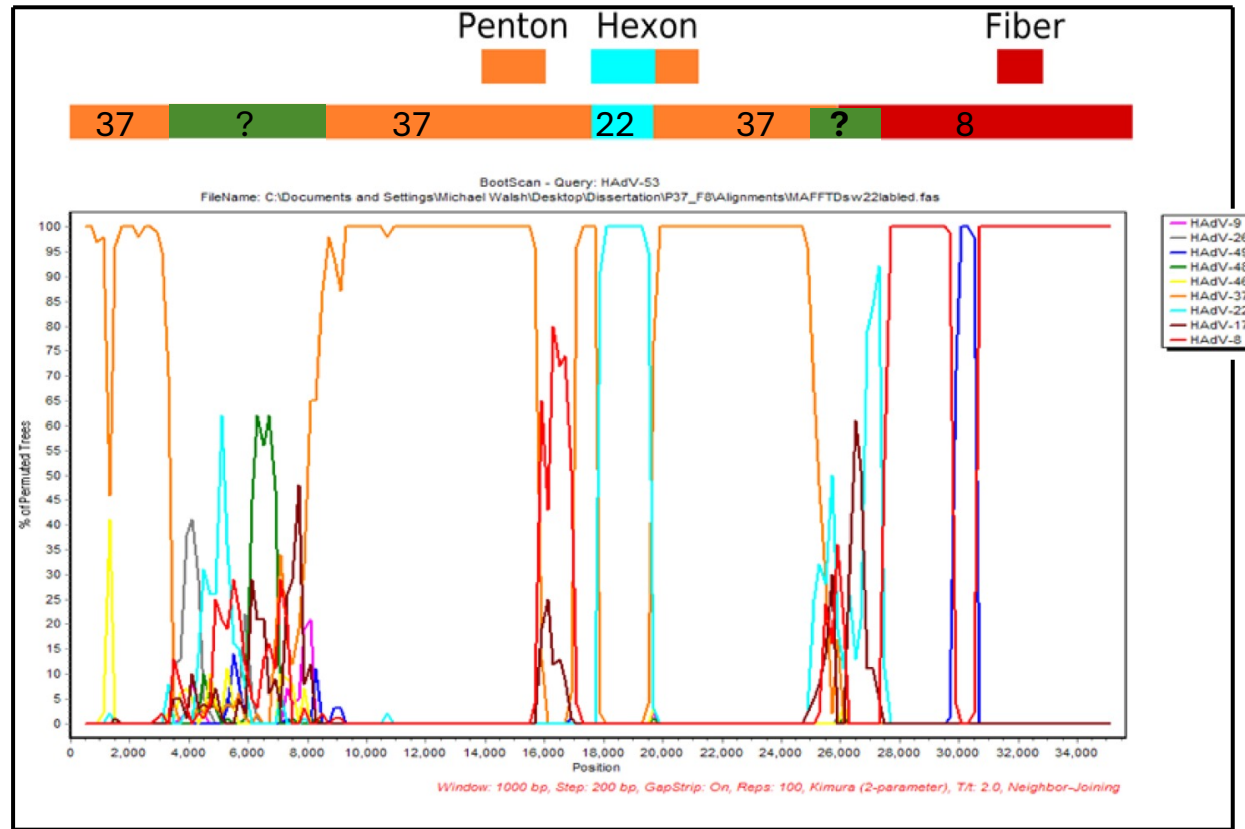
Donald Seto, James Chodosh, J Rodney Brister, Morris S Jones,
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We propose that human adenoviruses (HAdVs) be identified, characterized, and typed on the basis of complete genome sequence analyses rather than serological approaches. This

- Based on genome, penton base, hexon, and fiber
 - 100+ whole genomes in GenBank, 2011
 - Consistent with previous serology-based data*
 - Data/names compatible with databases, other viruses*
 - Recombinants constitute largest number of novel adenoviral pathogens
- Example- HAdV-53 is “Adenovirus D human/DEU/IAI-1/2005/53[P37H22F8]”



HAdV-53: “A new pathogen, a new type”



- Novel pathogen

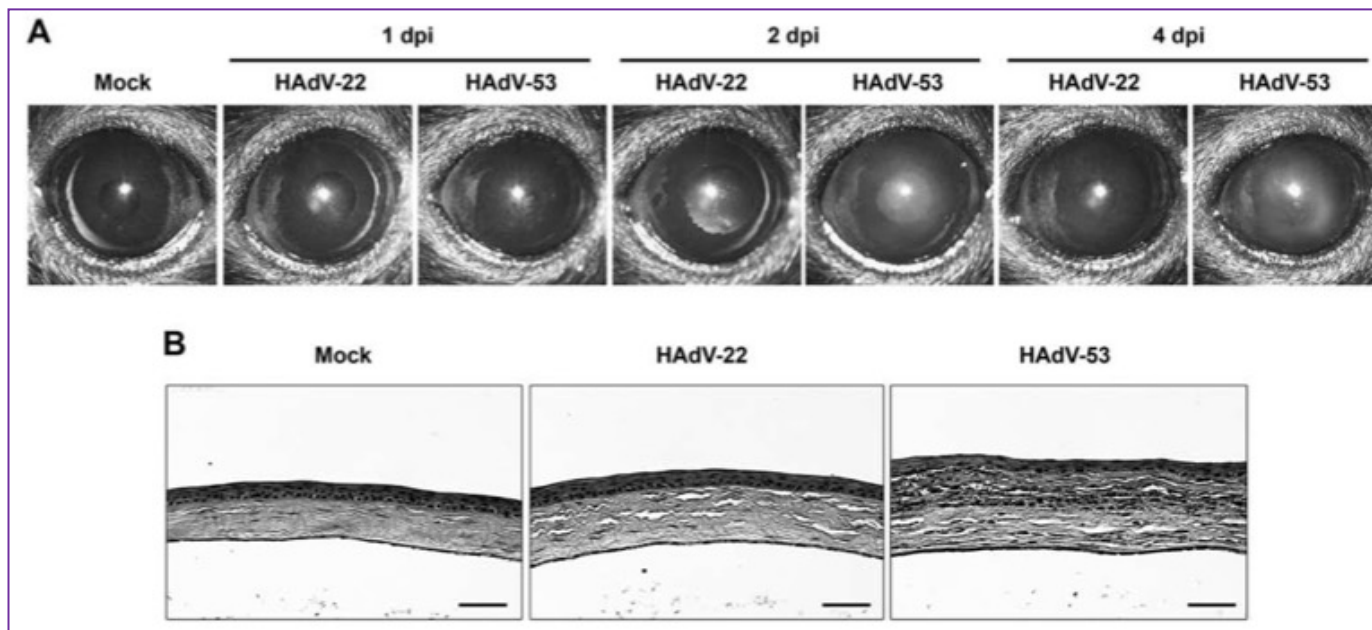
- HAdV-22 is not a pathogen; HAdV-53 isolated from Epidemic Keratoconjunctivitis outbreak, 2006

versus-

- 1) “It **has an ‘Ad22’ hexon, so it is ‘Ad22’** (‘and we only care which vaccine to use’)”
 - 2) “Recombinant is not a new type (*again-* M. Benko, 2023): Parentals are known; One occurrence”
- **Archived in Japan** ‘since 1996; 3rd most common; type 53 was “*misidentified*” as Ad8, Ad22, or Ad37’
- Kaneko, *et al.*, JCM (2011)

Novel pathogen: *in silico* to *in vivo*

- HAdV-53: Keratitis in a mouse cornea model
 - => “HAdV-22 is not an EKC pathogen”



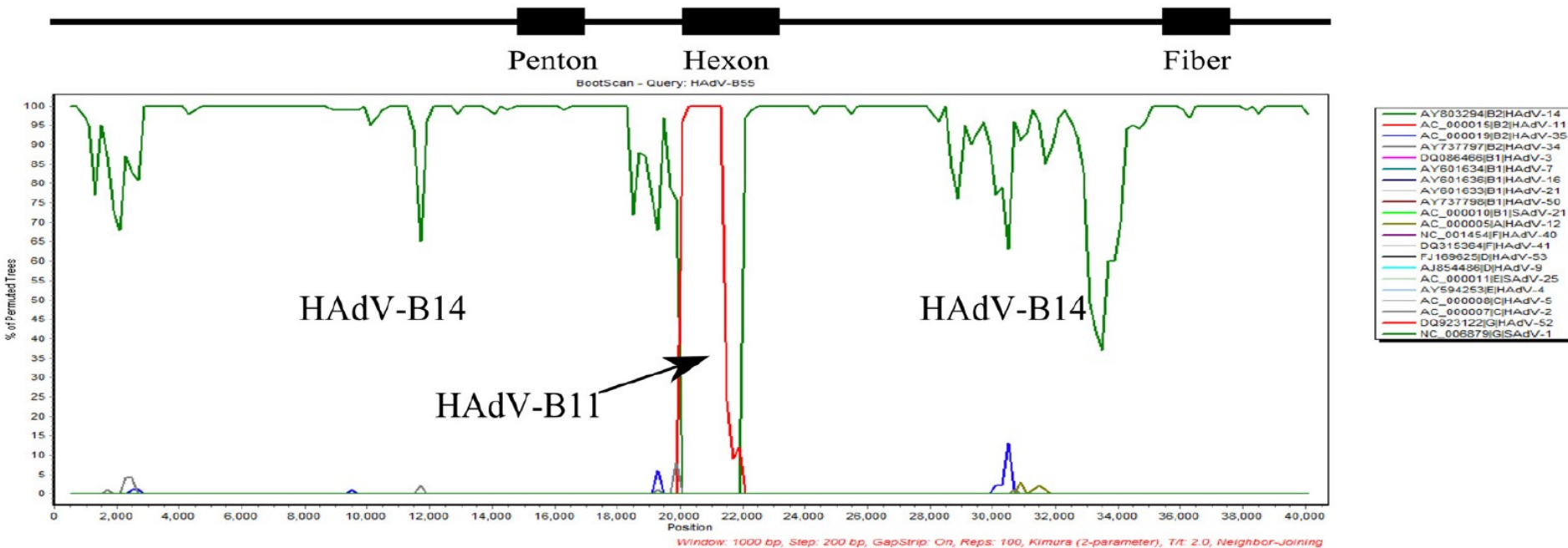
Evidence of molecular evolution driven by recombination events influencing tropism in a novel human adenovirus that causes epidemic keratoconjunctivitis.

Walsh MP, Chintakuntlawar A, Robinson CM, Madisch I, Harrach B, Hudson NR, Schnurr D, Heim A, Chodosh J, Seto D, Jones MS.

PLoS One. 2009 Jun 3;4(6):e5635. doi: 10.1371/journal.pone.0005635.

HAdV-55 (not 11a): “Pathology matters!” *not the hexon*

“...kidney \neq lung”



- Re-emergent pathogen

- HAdV-55 isolated from Acute Respiratory Disease outbreak, Shanxi Province 2009

[Computational analysis identifies human adenovirus type 55 as a re-emergent acute respiratory disease pathogen.](#)

Walsh MP, Seto J, Jones MS, Chodosh J, Xu W, Seto D.

J Clin Microbiol. 2010 Mar;48(3):991-3. doi: 10.1128/JCM.01694-09. Epub 2009 Dec 30.

“Are adenoviruses potential pandemic pathogens?”

THE EPOCH TIMES

Chinese Military Hospital in Lockdown Over Suspected SARS Cases

By Ming Chen

Epoch Times Staff

Last Updated: March 1, 2012 Created: February 27, 2012

Related articles: [China](#) » [Society](#)

TEXT SIZE   PRINT  EMAIL  FEEDBACK

- Acute Respiratory Disease outbreak?
 - 2012: Public and social media- “SARS?” !
- Baoding, Hebei Province
 - “Shops closed (‘for the first time, ever’) ... (‘for beautification & repainting’)”
 - PLA Hospital “removes civilian patients...”
 - “‘truckloads’ of military patients quarantined, with ‘guards posted’”
- No official information; no comments

SARS or ?

TABLE 1. Epidemiological characteristics of HAdV-related outbreak events of acute respiratory disease in military camps during December 2011–March 2014.

| Characteristic | All participants (N=13,622) | |
|---------------------------|-----------------------------|--------|
| | ARD patients (n=3,813) | P |
| Gender | | |
| Male | 3,720 (28.35) | <0.001 |
| Female | 93 (18.56) | |
| Age of soldier | | |
| New recruits | 2,722 (31.86) | <0.001 |
| Veterans | 1,091 (21.48) | |
| HAdV genotype | | |
| HAdV-B7 | 688 (24.77) | <0.001 |
| HAdV-B14 | 1,016 (37.70) | |
| HAdV-B55 | 2,109 (25.88) | |
| Outbreaks areas, province | | |
| HuBei/2013/HAdV-B7 | 376 (25.53) | <0.001 |
| ShanXi/2013/HAdV-B7 | 107 (16.54) | |
| HuBei/2013/HAdV-B7 | 205 (31.16) | |
| LiaoNing/2012/HAdV-B14 | 185 (30.32) | |
| GanSu/2013/HAdV-B14 | 831 (39.86) | |
| HeBei/2012/HAdV-B55 | 650 (28.54) | |
| ShanXi/2011/HAdV-B55 | 309 (10.92) | |
| TianJin /2012/HAdV-B55 | 1,150 (37.80) | |
| Total | 3,813 (27.99) | |

Note: The information on the ninth outbreak of Liaoning /2013/ HAdV-B55 was missing.

- Acute Respiratory Disease outbreak
 - 2012: ‘*Please identify this virus.*’
 - \approx HAdV-55, Shanxi Province 2009
 - ‘Can we publish this?’ – ‘No’
- 2021 “retrospective” publication
 - Morbidity and mortality?

Outbreaks of Acute Respiratory Disease Associated with Human Adenovirus Infection in Closed Camps, China, December 2011–March 2014.

Du J, Zhao X, Tang F, Huang D, Pei G, Zhang X, Jiang B, Lu Q, Liu W, Tong Y. China CDC Wkly. 2021 Sep 17;3(38):793–798. doi: 10.46234/ccdcw2021.197.

“Are adenoviruses potential pandemic pathogens?”

ASIANSCIENTIST

March 30, 2023 • [Health, Top News](#) • By [Puja Bhattacharjee](#)

Adenovirus Outbreak Has Infected Thousands Of Children In India

Researchers recommend monitoring adenovirus mutations and developing vaccines.

AsianScientist (Mar. 30, 2023) — An Adenovirus outbreak in India’s eastern state of West Bengal infected more than 12,000 children between January and March this year. This outbreak was unprecedented in scale and severity.

Adenovirus infection cases were also reported in other cities such as Mumbai, Pune, Bangalore, and Jaipur, but the situation in West Bengal was dire. According to the government statistics, the death toll is 19. However, paediatricians say that more than 150 children have died due to Adenovirus infections and related complications.

National Institute of Cholera and Enteric Diseases (NICED) in Kolkata analyzed genetic makeup of the Adenovirus samples collected from the affected children to ascertain the serotype of the virus. The serotype tells us how viruses are grouped based on the type of surface antigen present. The surface antigens enable bacterial attachment and invasion of host cells and the evasion of host immune defense mechanisms. The serotype analysis showed that the serotypes 3 and 7 and the recombinant strain 7/3 (the strain made by combining genetic material from type 3 and type 7), were found in most cases in West Bengal.

- Acute Respiratory Disease outbreak(s)
ca., 2022-2023; Public media
- => **Serotypes 3, 7, and 7/3**
- Morbidity and mortality?

“Adenovirus lineage evolution”, Types 3 and 66 (7h?)

| Patient ID | WG Homology | Genotype Based on, Hexon Fiber, Penton Genes | Co-Infection | ICU Admission | Oxygen Requirement | Final Outcome |
|------------|------------------------|--|--------------|---------------|--------------------|---------------|
| 1914 | 3 (KF268210.1, 99.21%) | 3[H3F3P7] | No | No | No | Recovered |
| 1908 | 7 (KF268125.1, 99.25%) | 7[H7F3P7] | No | Yes | Yes | Recovered |
| 2280 | 7 (KF268125.1, 99.21%) | 7[H7F3P7] | PIV | Yes | Yes | Death |
| 2283 | 7 (KF268125.1, 99.25%) | 7[H7F3P7] | No | Yes | Yes | Death |
| 2220 | 7 (KF268125.1, 99.14%) | 7[H7F3P7] | No | Yes | Yes | Death |
| 2213 | 7 (KF268125.1, 99.28%) | 7[H7F3P7] | Rhino | No | No | Recovered |
| 1995 | 7 (KF268125.1, 99.26%) | 7[H7F3P7] | No | No | No | Recovered |
| 1836 | 7 (KF268125.1, 99.16%) | 7[H7F3P7] | No | No | Yes | Recovered |
| 1639 | 7 (KF268125.1, 99.24%) | 7[H7F3P7] | No | Not Available | Not Available | Not Available |
| 2640 | 7 (KF268125.1, 99.19%) | 7[H7F3P7] | No | Yes | Yes | Death |
| 2788 | 7 (KF268125.1, 99.23%) | 7[H7F3P7] | No | Not Available | Not Available | Not Available |
| 2908 | 3 (KF268132, 97.75%) | 3[H7F3P7] | No | Yes | Yes | Recovered |
| 2909 | 3 (AY599834.1, 99.35%) | 3[H3F3P3] | No | Yes | Yes | Recovered |

• Acute Respiratory Disease outbreak(s)

=> HAdV-3 and *two* recombs, *or 3?*: P7H7F3 and P7H3H3, and P7H3F3?

• 2023-2024 “research” publications (*three*)

• Morbidity and mortality (last entry ID 3289)?

Genomic Expedition: Deciphering Human Adenovirus Strains from the 2023 Outbreak in West Bengal, India: Insights into Viral Evolution and Molecular Epidemiology.

Chatterjee A, Bhattacharjee U, Gupta R, Debnath A, Majumdar A, Saha R, Chawla-Sarkar M, Chakrabarti AK, Dutta S.

Viruses. 2024 Jan 21;16(1):159. doi: 10.3390/v16010159.

Community resource: Reference and standards

HAdV Working Group

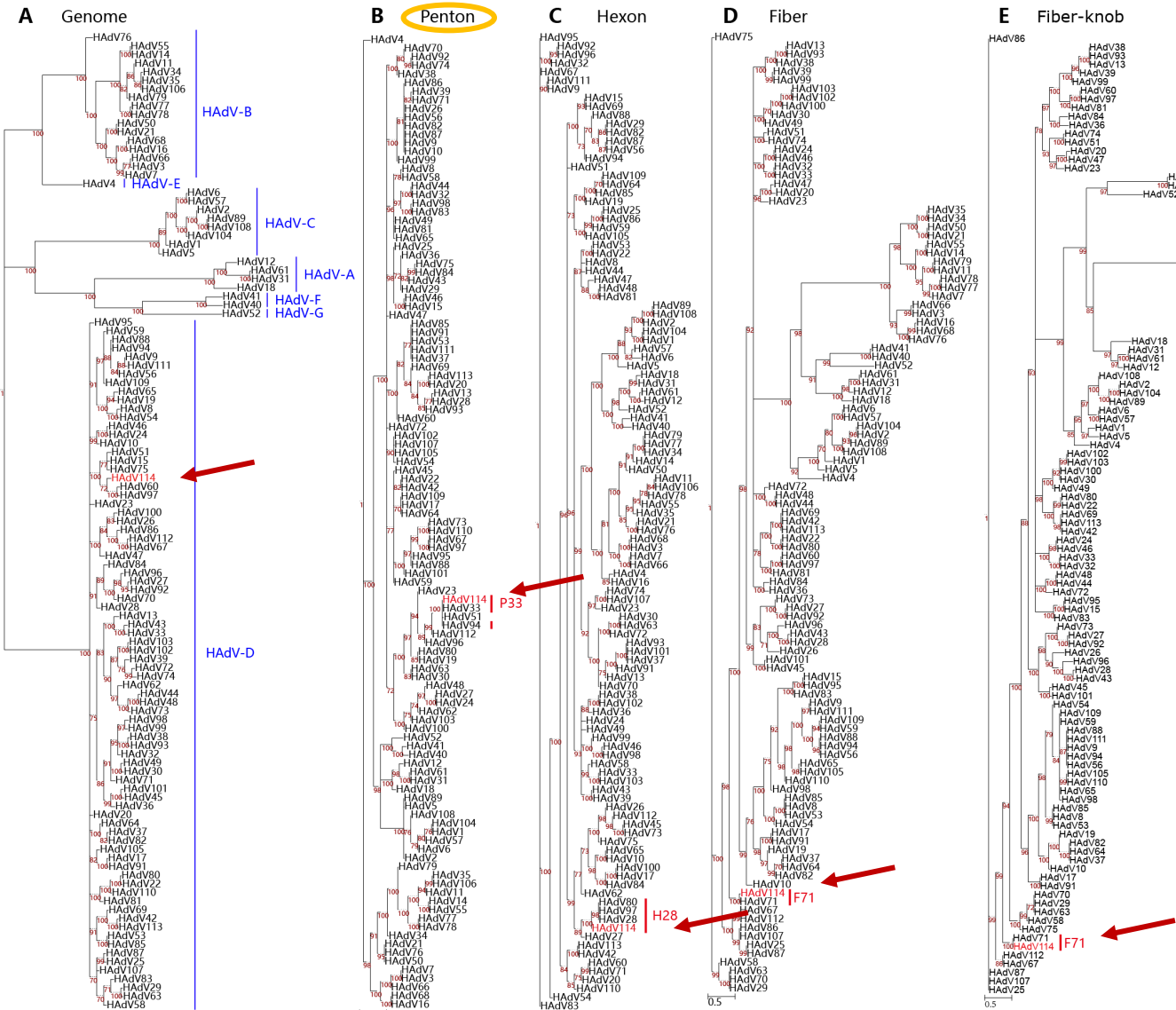


[Home](#) [About](#) [Background](#) [Criteria for a New HAdV Type](#) [Submit “candidate” HAdV](#) [Serotyping Tool](#) [Tools](#) [Contacts](#)

| Adenovirus Genotype | Name | Accession # | Year (Publication) | Penton base | Hexon | Fiber |
|------------------------|-----------|-------------|-----------------------|----------------|-------|-------|
| HAdV-D116 | P33H28F71 | TBA | 2024 | 33 | 28 | 71 |
| HAdV-D115 | P22H8F8 | OR044915 | 2024 | 22 | 8 | 8 |
| HAdV-B114 | P7H3F3 | OR853835 | 2023 | 7 | 3 | 3 |
| HAdV-D113 | P20H42F42 | MW694832 | 2021 | 20 | 42 | 42 |

•2010, Rodney Brister (NCBI); <http://hadvwg.gmu.edu> => “There will be too many numbers!” –B. Harrach

HAdV-116, species D as novel pathogen? -encephalitis



- *Not* HAdV-114 ⇒ Assigned to P7/H3/F3 (submitted with “novel” P7/H7/F3 (“HAdV-66”))
- Wenjing Chen; Vision Medicals Center for Infectious Diseases, Guangzhou (China); Fall 2023

Acknowledgments

Program of Bioinformatics and Computational Biology, School of Systems Biology (SSB), George Mason University (Manassas, Virginia)

Marwy El Attar

Divyasphoorthi Vardhan

Katayoon Dadkhan

Daniel Negrón (Noblis, Inc.)

June Kang (Noblis, Inc.)

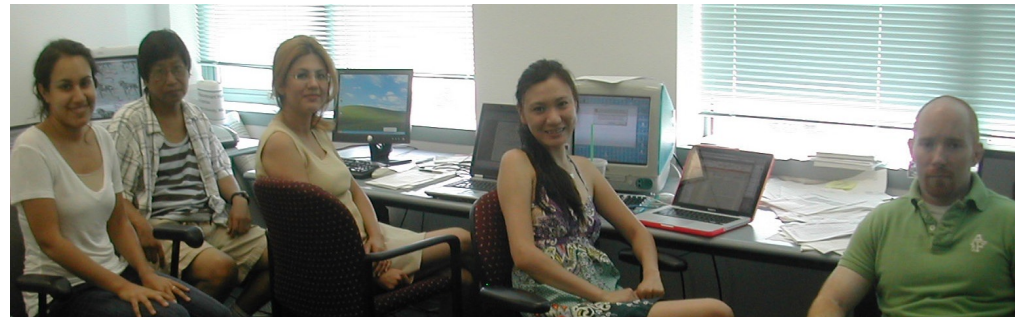
Kalpana Dommaraju (WRAIR)

Elizabeth B. Liu (GWU)

Michael P. Walsh (St. Jude Children's Research Hospital)

Padmanabhan Mahadevan (University of Tampa)

Jason Seto



HAdV working group (2010 - present)

James Chodosh, Albert Heim, Thomas Lion, Morris S. Jones, Adriana Kajon, Qiwei Zhang; J. Rodney Brister and Olga Blinkova (NCBI)

Colleagues/collaborators

Shoaleh Dehghan (American University; WA DC, USA)

Qiwei Zhang (Jinan University; Guangzhou, China)

Albert Heim (Medizinische Hochschule; Hannover, Germany)

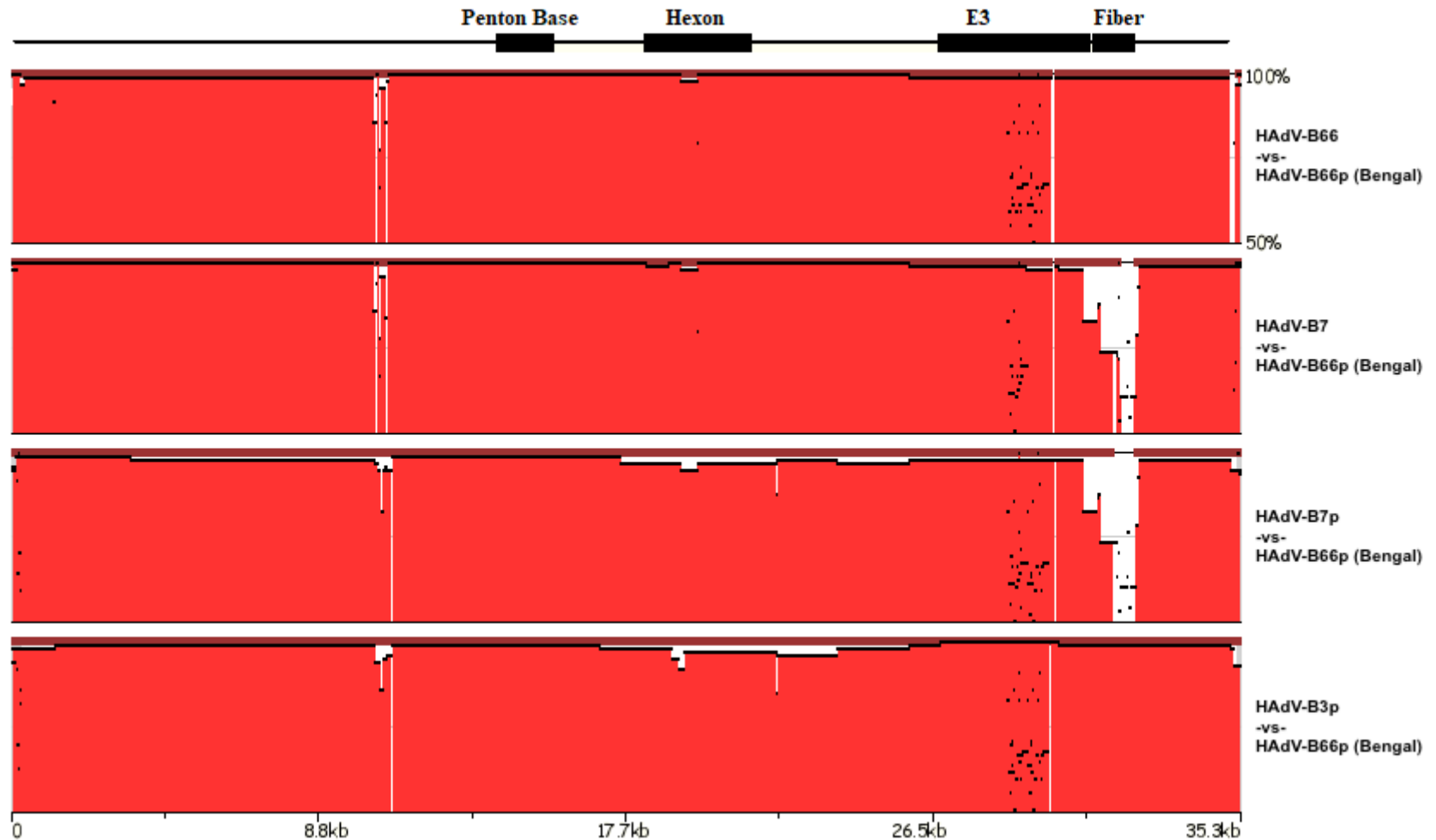
David W. Dyer (University of Oklahoma; Oklahoma City, USA)

James Chodosh (University of New Mexico; Albuquerque, USA)

Genome %ID

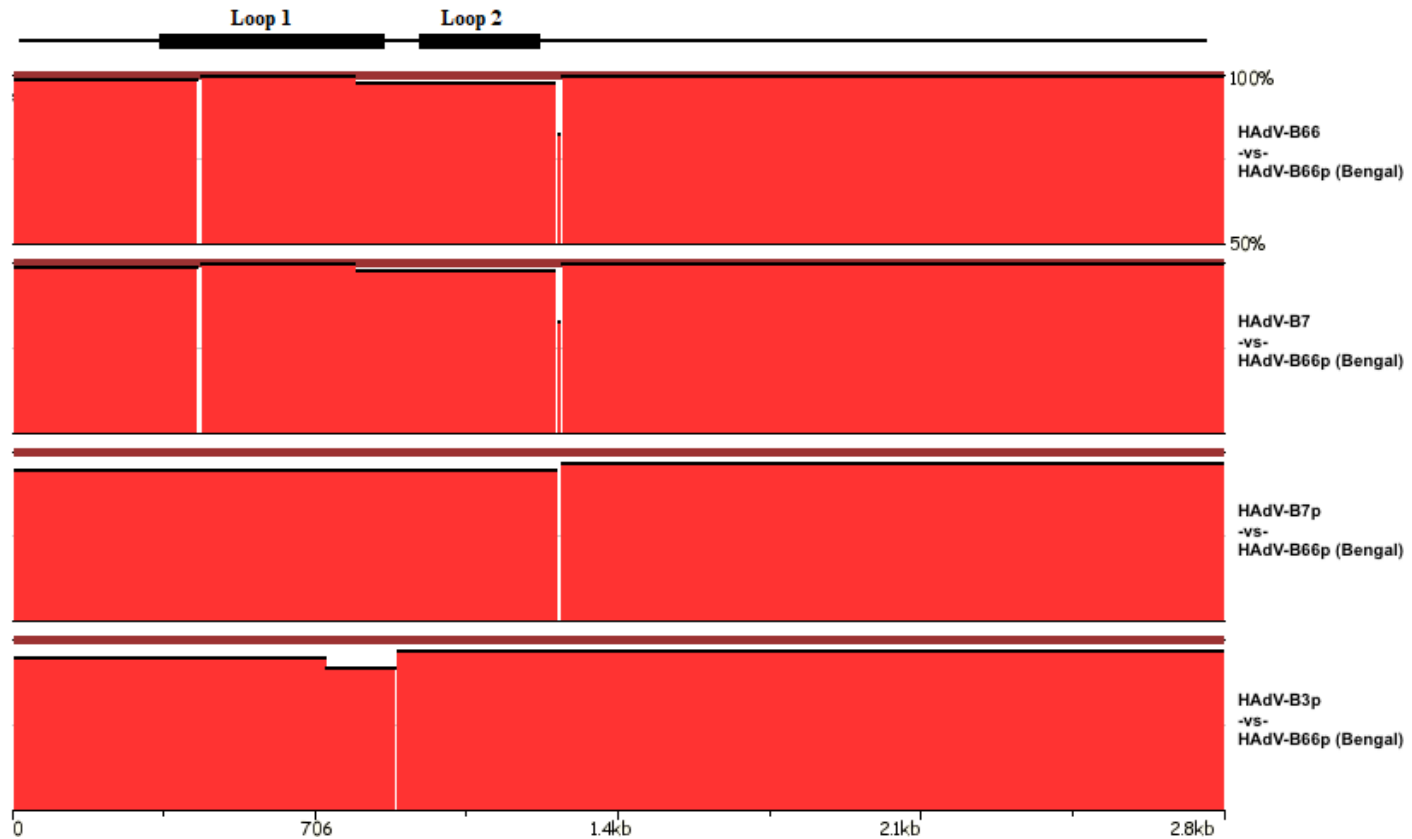
| | 66 | 66Bengal | 3p |
|-----------------|-----------|-----------------|-----------|
| 7p | 95.80% | 96.30% | 96.40% |
| 66 | | 98.10% | 97.80% |
| 66Bengal | | | 97.80% |

“Bengal recombinant is highly similar to HAdV-66”



- Bengal 2023 is highly similar to HAdV-66, 1987 @98.1%
- Bengal 2023 is highly similar to HAdV-B7, 1997
- Bengal 2023 and HAdV-66, 1987 similar to HAdV-7p, 1952 @95.8%
-and similar to HAdV-3p, 1952 97.8%

“Recent recombination” *ca*, 1997



- Hexon is highly similar to HAdV-66, 1987, and HAdV-B7, 1997 vs HAdV-7p, 1952

“Recent recombination”, but not HAdV-66 exactly!

Loop 1

| | |
|--------------------|---|
| HAdV-B66p (Bengal) | Y S G T A Y N S L A P K G A P N T S Q W I V T T N R D N A V T T T T Y T F G I A S T K G D N I T K E G L E I G K D I T A D N - - - K P I Y A |
| HAdV-B3p | Y S G T A Y N S L A P K G A P N T S Q W I V T T N G D N A V T T T T N T F G I A S M K G D N I T K E G L Q I G K D I T T T E G E E K P I Y A |
| HAdV-B7p | Y S G T A Y N S L A P K G A P N T S Q W I V T A G E E R A V T T T T N T F G I A S M K G D N I T K E G L E I G K D I T A D N - - - K P I Y A |
| HAdV-B7 | Y S G T A Y N S L A P K G A P N T S Q W I V T T G E D N - - - A T T Y T F G I A S T K G D N I T K E G L E I G K D I T A D N - - - K P I Y A |
| HAdV-B66 | Y S G T A Y N S L A P K G A P N T S Q W I V T T G E D N - - - A T T Y T F G I A S T K G D N I T K E G L E I G K D I T A D N - - - K P I Y A |

| | |
|--------------------|---|
| HAdV-B66p (Bengal) | D K T Y Q P E P Q V G E E S W T D I D G T N E K F G G R A L K P A T K M K P C Y G S F A R P T N I K G G Q A K N R K V T P - T E G D V E A E |
| HAdV-B3p | D K T Y Q P E P Q V G E E S W T D T D G T N E K F G G R A L K P A T N M K P C Y G S F A R P T N I K G G Q A K N R K V K P T T E G G V E T E |
| HAdV-B7p | D K T Y Q P E P Q V G E E S W T D T D G T N E K F G G R A L K P A T K M K P C Y G S F A R P T N I K G G Q A K N R K V K P - T E G D V E T E |
| HAdV-B7 | D K T Y Q P E P Q V G E E S W T D I D G T N E K F G G R A L K P A T K M K P C Y G S F A R P T N I K G G Q A K N R K V T P - T E G D V E A E |
| HAdV-B66 | D K T Y Q P E P Q V G E E S W T D I D G T N E K F G G R A L K P A T K M K P C Y G S F A R P T N I K G G Q A K N R K V T P - T E G D V E A E |

| | |
|--------------------|---|
| HAdV-B66p (Bengal) | E P D I D M E F F D G R E A V A G A L A P E I V L Y T E N V N L E T P D S H V V Y K P G T S D G N S H A N L G Q Q A M P |
| HAdV-B3p | E P D I D M E F F D G R D A V A G A L A P E I V L Y T E N V N L E T P D S H V V Y K P E T S N - N S H A N L G Q Q A M P |
| HAdV-B7p | E P D I D M E F F D G R E A A D - A F S P E I V L Y T E N V N L E T P D S H V V Y K P G T S D D N S H A N L G Q Q A M P |
| HAdV-B7 | E P D I D M E F F D G R E A A D - A F S P E I V L Y T E N V N L E T P D S H V V Y K P G T S D G N S H A N L G Q Q A M P |
| HAdV-B66 | E P D I D M E F F D G R E A A D - A F S P E I V L Y T E N V N L E T P D S H V V Y K P G T S D G N S H A N L G Q Q A M P |

Loop 2

| | |
|--------------------|---|
| HAdV-B66p (Bengal) | I E N H G V E D E L P N Y C F P L D G I G P G N K Y Q Q I K V K T D D A N G W E K D T K V S T A N E I A I G N N L A M E |
| HAdV-B3p | I E N H G I E D E L P N Y C F P L N G I G P G H T Y Q Q I K V K T D D T N G W E K D A N V A P A N E I T I G N N L A M E |
| HAdV-B7p | I E N H G I E D E L P N Y C F P L D G I G P A K T Y Q Q I K S K - - - D N G W E K D D N V S K S N E I A I G N N Q A M E |
| HAdV-B7 | I E N H G V E D E L P N Y C F P L D G I G P G N K Y Q Q I K P R - D T A - - W E K D T K V Y T A N E I A I G N N L A M E |
| HAdV-B66 | I E N H G V E D E L P N Y C F P L D G I G P G N K Y Q Q I K P R - D T A - - W E K D T K V S T A N E I A I G N N L A M E |

| | |
|--------------------|---|
| HAdV-B66p (Bengal) | I N I Q A N L W R S F L Y S N V A L Y L P D V Y |
| HAdV-B3p | I N I Q A N L W R S F L Y S N V A L Y L P D V Y |
| HAdV-B7p | I N I Q A N L W R S F L Y S N V A L Y L P D V Y |
| HAdV-B7 | I N I Q A N L W R S F L Y S N V A L Y L P D V Y |
| HAdV-B66 | I N I Q A N L W R S F L Y S N V A L Y L P D V Y |

- Hexon is highly similar to HAdV-3p, 1952 (black, orange, blue boxes), and
- But to** HAdV-66 (1987), HAdV-B7 (1997), HAdV-7p, 1952 (red, green boxes)
- => intra-hexon recombination?