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Computational analysis of four human adenovirus type 4 genomes reveals molecular evolution through two interspecies recombination events

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ABSTRACT

Computational analysis of human adenovirus type 4 (HAdV-E4), a pathogen that is the only HAdV member of species E, provides insights into its zoonotic origin and molecular adaptation. Its genome encodes a domain of the major capsid protein, hexon, from HAdV-B16 recombined into the genome chassis of a simian adenovirus. Genomes of two recent field strains provide a clue to its adaptation to the new host: recombination of a NF-I binding site motif, which is required for efficient viral replication, from another HAdV genome. This motif is absent in the chimpanzee adenoviruses and the HAdV-E4 prototype, but is conserved amongst other HAdVs. This is the first report of an interspecies recombination event for HAdVs, and the first documentation of a lateral partial gene transfer from a chimpanzee AdV. The potential for such recombination events are important when considering chimpanzee adenoviruses as candidate gene delivery vectors for human patients.

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Introduction

Adenoviruses are found in many vertebrate hosts, spanning fish to human (Benkö et al., 2005; Davison et al., 2003). Human adenoviruses (HAdVs) may be pathogens, causing symptoms ranging from mild to severe, including death. They may also infect asymptomatically and persistently (Garnett et al., 2009), and are found to coinfect with other HAdVs, with up to four viruses characterized in some patients (Barrero et al., 2012; Metzgar et al., 2005; Vora et al., 2006). A wide spectrum of diseases are reported, involving the respiratory, ocular, gastrointestinal and genitourinary systems, as well as a metabolic disorder (obesity) (Echavarria, 2008). Since the initial nearly simultaneous reports of HAdVs as respiratory pathogens in 1953 (Hilleman and Werner, 1954; Rowe et al., 1953), they have been examined extensively, leading to insights in cell biology, molecular biology, immunology and epidemiology, as noted in a report of the 10th International Adenovirus Meeting in 2012 (Umea, Sweden) (Greber et al., 2013). Reflecting their importance in health and biotechnology, new HAdVs continue to be identified and characterized at high-resolution using genomics, albeit with some disagreement on using whole genome data to characterize, type and classify candidate new types (Seto et al., 2011) rather than serology-based methods (Aoki et al., 2011).

All of the HAdV prototype genomes are now completely sequenced (manuscript submitted for publication), providing a reference data set for comparative analyses amongst these prototypes, other archived historically important HAdVs and newly emergent HAdV strains. Detailed understanding of how these new pathogens emerged has come from such analyses. For example, an emergent highly contagious keratoconjunctivitis (EKC) pathogen (Engelmann et al., 2006) was revealed as a recombinant with at least three parents (Walsh et al., 2009); an emergent acute respiratory disease (ARD) pathogen causing a fatality and subsequent transmission as a highly contagious ocular disease pathogen (Henquell et al., 2009) was revealed as a recombinant (Robinson et al., 2011); and a re-emergent ARD pathogen that has the serological profile of a renal tract pathogen (Yang et al., 2009; Zhu et al., 2009) was revealed as a recombinant with two parents (Walsh et al., 2010).

Adenoviruses are important biomedical tools as vectors for epitope and gene delivery (Darr et al., 2009; Fujishiro et al., 2005; Graham and Prevec, 1992; Stone et al., 2006). Serendipitously, the

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recent attention to non-human simian adenoviruses (SAdVs) in this capacity has brought additional genomes into the data set (Roy et al., 2004a, 2004b, 2012, 2009, 2006), complementing the HAdV genomes and allowing for higher resolution into origins of other HAdVs. One example is HAdV-E4, which has been shown to contain a genome with relatively high similarity to several chimpanzee adenoviruses (Purkayastha et al., 2005a). HAdV-E4 is an important respiratory and ocular pathogen, as one of two HAdVs warranting a vaccine in the 1960s and again recently (Gaydos and Gaydos, 1995; Kajon et al., 2007; Lyons et al., 2008; Russell et al., 2006). Its origins were probed in different eras with then-available and then-novel protocols and instruments, including serological cross-reactivity of both its hexon and fiber; protein chemistry measurements (i.e., molecular weights of "internal polypeptides"); limited peptide sequencing (N-terminal amino acids); and limited nucleotide sequence analysis, e.g., restriction enzyme digests (Adrian et al., 1986; Gruber et al., 1993; Li and Wadell, 1988; Norrby and Wadell, 1969; Wadell, 1984). Recently, limited nucleotide sequencing of the putative epsilon epitope that contributes to its serum neutralization has provided additional clues about its phylogenetic relationships and origins (Ebner et al., 2005; Madisch et al., 2005; Pring-Akerblom et al., 1995; Sarantis et al., 2004). Speculations that HAdV-E4 directly derived from a putative common ancestor of HAdVs, is a recombinant of species B and C, or is related to chimpanzee adenoviruses were based on these limited data sets (Gruber et al., 1993; Li and Wadell, 1988; Wadell, 1984). Later, with its genome sequenced and a newly available set of SAdVs (Purkayastha et al., 2005a, 2005b; Roy et al., 2004a) for comparison, a definitive zoonotic origin was revealed based on nucleotide and amino acid sequence identities (Purkayastha et al., 2005a). With the recent upload of additional SAdV genomes into the public database (Roy et al., 2009), a more complete and granular understanding emerges, as reported here. The HAdV-E4 genome is a recombinant that contains the hexon loops 1 and 2 (L1 and L2) of HAdV-B16, comprising approximately 2.5% of the whole genome, in a genome chassis of SAdV-E26, similar to the genome structure reported for the re-emergent recombinant respiratory pathogen HAdV-B55 (Walsh et al., 2010). Included in this report are the computational analyses of two more recent HAdV-E4 field strains that provide an additional view as to the mechanism of how this virus adapted to the human host: A recombination that provides the NF-I binding motif, which is conserved across all other HAdVs as part of the DNA replication motifs, from a species B2 HAdV distinguishes these two recent isolates. Notably, this motif is either absent amongst the chimpanzee adenoviruses and both the type 4 prototype (HAdV-E4p) and the then-contemporary field strain (HAdV-E4vac) genomes (Purkayastha et al., 2005a, 2005b) or is a version that is unique to the chimpanzee adenoviruses.

Results

Comparative genomic analysis

The genomes of HAdV-E4 field strains (FS) isolated recently from two U.S. military basic trainees at separate geographic locations and presenting with ARD were sequenced, analyzed, and compared with genomes from strains isolated approximately 60 years ago. Table 1 provides details of these strains.

Computational analysis confirmed both field strain viruses as HAdV-E4 genomes and as being highly similar to each other. Alignments of the genomes using Sequencher and MEGA showed there are 46 base substitutions and seven indels, comprising five

Table 1
HAdV-E4 strains. Details of the type 4 viruses are presented, including alternative names, year of isolation, location of isolation, GenBank accession number, and the genome size.

HAdV-E4 strains							
Strain	Designation	Alt. name	Alt. name	Isol. yr.	Location isol.	Acc. no.	Genome size
Prototype	HAdV-E4p	RI-67		1952	Ft. Wood, MO	AY594253	35,990
Vaccine	HAdV-E4vac	Wyeth		1962	Camp Lejune, NC	AY594254	35,994
Field strain 1	HAdV-E4FS1	NHRC 42606	HAdV-E4a2	2003	Ft. Jackson, SC	AY599835	35,965
Field strain 2	HAdV-E4FS2	NHRC 3	HAdV-E4a1	2002	Brooks AFB, TX	AY599837	35,964

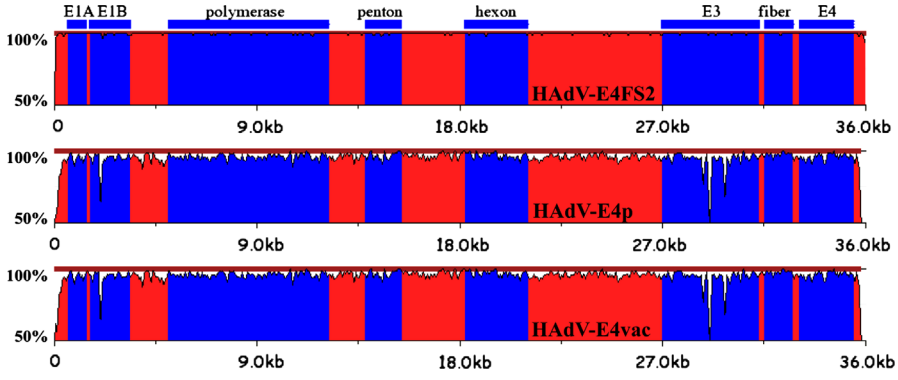

Fig. 1. Pairwise genome comparative analysis. zPicture (http://zpicture.dcode.org/) utilizes a local alignment algorithm, BlastZ, to display the regions of nucleotide sequence similarity between HAdV-E4FS1 and query genomes: HAdV-E4FS2 (top); HAdVE4p (middle); and HAdV-E4vac (bottom). Of note are the divergences at the ends of the genomes, corresponding to the semi-conserved inverted terminal repeat (ITR) sequences that contain critical functions, including DNA replication. The genome sequences are arrayed on the horizontal and the percent identity of genome pairs from 50% to 100% is noted along the *y*-axis. The colors are arbitrary and are used to provide contrast: blue regions highlight select genes or genome regions (E3), noted above the alignments. Red regions include both coding and noncoding sequences.

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