



Challenges in management of epidemic keratoconjunctivitis with emerging recombinant human adenoviruses

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ABSTRACT

Adenoviral epidemic keratoconjunctivitis (EKC) presents as severe conjunctival inflammations involving the cornea that can lead to the development of corneal opacities and blurred vision, which can persist for months. EKC is highly contagious and responsible for outbreaks worldwide, therefore accurate diagnosis and rapid containment are imperative. EKC is caused by a number of types within *Human adenovirus* species D (HAdV-D): 8, 37 and 64 (formerly known as 19a) and these types were considered the major causes of EKC for over fifty years. Nonetheless, recent improved molecular typing methodologies have identified recombinant HAdV-D types 53, 54 and 56, as newly emerging etiologic agents of EKC infections worldwide. EKC cases due to these recombinant types have potentially been underdiagnosed and underestimated as a source of new EKC outbreaks. Recombination events among circulating HAdV-D types represent a source of new infectious disease threats. Also, the growing number of adenoviral types enabled genomic and phenotypic comparisons to determine pathological properties related to EKC. This review covers the clinical features of EKC, current challenges in clinical practice and recent progress in EKC-related HAdV research, which focuses on the development of novel diagnostic and therapeutic approaches.

1. Introduction

Human adenovirus (HAdV) strains are the source of multiple infections in human populations worldwide, including ocular infections, with a broad range of severity [1]. Adenoviral conjunctivitis is caused mainly by HAdV-B 3; HAdV-C 1, 5, and 6; HAdV-D 8, 19a (renamed 64), 37, 53, 54, and 56 [2–7]; and HAdV-E 4. Epidemic keratoconjunctivitis (EKC) is a major cause of ocular morbidity in developed and developing countries and no efficacious therapeutic options are available [8]. HAdV-8 was the first type isolated from an American patient with EKC in 1954, who had recently returned from Asia [9,10]. HAdV-64 was subsequently identified in 1973 [11,12] and HAdV-37 in 1976 [13,14]. For over half a century, these three viral types (HAdV-8, 37 and 64) have been considered the major causes of EKC outbreaks worldwide [15–18].

Analysis of data collected by the Japanese surveillance system for ocular infections over the last 30 years, reveals a steady increase in the

frequency of EKC cases involving the novel adenoviral types 53, 54, and 56 (Fig. 1), since their first report in 2008 [19]. The outbreaks caused by recombinant strains in Asia, America, and Europe, has led to an increased awareness of the need for global surveillance and disease control [20]. Current efforts to establish comprehensive criteria in EKC diagnosis, development of antiviral treatments and prevention measures against outbreaks are urgently required. This review covers the clinical features of EKC, the current challenges in clinical practice, and recent progress of EKC-related HAdV research, which will help to inform the development of novel diagnostic and therapeutic approaches.

2. Clinical features of adenoviral epidemic keratoconjunctivitis and challenges for diagnosis

The common symptoms of EKC include severe hyperemia, diffuse infiltration, lacrimation, follicular conjunctivitis, pseudomembrane formation with potential permanent symblepharon formation or

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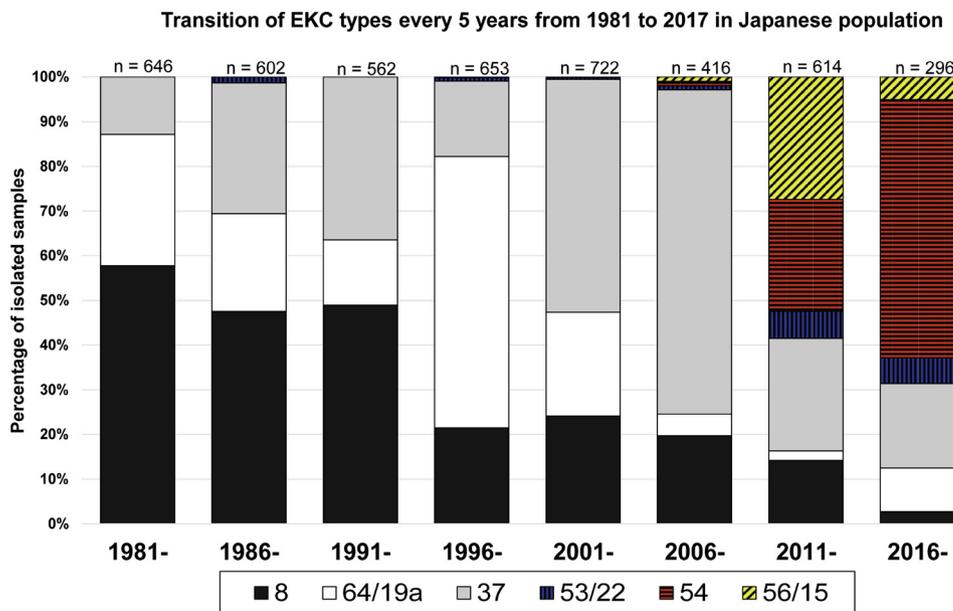


Fig. 1. Transition of EKC causative agents in Japan between 1981 and 2017. The samples were isolated and reported by the Japanese infectious disease surveillance system. As detection methodologies and the numbers of sentinel centers changed over the time period of interest, percentages were compared. Each bar shows the percentage of isolated samples per HAdV type over a period of 5 years starting with the year shown on the horizontal axis. The total number of cases is shown on the top of each bar.

punctual occlusion, and regional lymphadenopathy, such as mild swelling of the preauricular nodes [1,15,21]. In some cases, flu-like symptoms are presented such as myalgia and fever [1]. If the infection extends to the cornea, filamentous keratitis, corneal erosion, and ulceration can occur, followed by the formation of multiple subepithelial corneal infiltrates (MSIs), which is induced by inflammatory response [22,23]. The spotted opacities under the corneal epithelium can persist for several weeks to months, even years and result in visual decline, glare sensation, photophobia, and irregular astigmatism [1,23,24]. Magnetic resonance imaging of a typical EKC case revealed an inflammatory process that extends surprisingly deep into the orbit [25]. A study of 102 suspected EKC cases suggested that acute bilateral follicular conjunctivitis, intrafamilial infection, and MSI are strong indicators of EKC in the early stage of infection [15]. However, it should be noted that > 50% of EKC cases do not present MSI.

The EKC incubation period varies between 2 days and 2 weeks, and patients become contagious after the onset of symptoms for up to 2 weeks thereafter [26]. The signs of conjunctivitis show at the first stage, and MSIs are observed within 7–10 days after the onset of infection [27]. Although both eyes are easily infected due to the highly infective nature of adenoviruses, symptoms are generally more intense in the firstly infected eye [26].

Infections by other agents, such as *Chlamydia trachomatis*, herpes simplex virus, Coxsackievirus group type A24 variant (CVA24v), and Enterovirus 70 (E70), exhibit similar symptoms to EKC and are sometimes difficult to distinguish and treat [21]. Punctate hemorrhage in the palpebral conjunctiva is characteristic of adenoviral EKC and can be distinguished from the multiple spots of small hemorrhage on the bulbar conjunctiva in acute hemorrhagic conjunctivitis (AHC) caused by E70 or CVA24v. Although pseudomembranous conjunctivitis is frequently observed in pediatric EKC, it also can be caused by chlamydia, possibly because the conjunctival epithelial cell layer is still immature in infants. HAdV-8, 37, 53, 56, and 64, have been isolated also in sexually transmitted disease clinics in cases of genital ulcers and urethritis, suggesting eyes and urinary organs serve favorable conditions for the spread of the EKC-related HAdVs [28–31].

In this moment we have no perfect diagnostic method of EKC clinically and etiologically, current methods are based on antigen detection by immunofluorescence or immunochromatography [32–34], culture isolation [35], and molecular methods such as polymerase chain reaction (PCR), either home brew [36,37] or commercial kits such as adenovirus r-gene [38]. Although immunochromatography kits based

on antigen detection are relatively cheap and can be used at clinics with results in 10 min [39], they are limited by the stage of the infection and the number of viral copies present in the eye with 88–91% sensitivity [40]. Virus isolation in cell line cultures (A549, Hep-2 and HeLa) is used in epidemiological studies of EKC, however, it is time-consuming (2 to > 21 days in some samples) [41,42] and thus not useful in clinics. Furthermore, results may be noninterpretable if contaminated with other pathogens [38]. Molecular methods, such as conventional PCR and real time PCR, are highly sensitive and provide accurate results in short times; however, besides requiring equipment inaccessible to general clinics, the heterogeneity among various types limits the development of universal primers. In addition, proper typing of samples and recombination detection are performed by genome sequencing, which can be time-consuming and costly, limiting its usage to epidemiological studies [43].

Adenovirus identification on samples based solely on the hexon such as antisera neutralization and partial sequencing of its coding region leads to mistyping of recombinant types. Furthermore, data for Fig. 1 shows prior to the characterization of genotypes 53, 56 and 64 as recombinant types, infections by these genotypes were attributed to the recombinant parental types 22, 15 and 64, respectively, by anti-sera and partial sequencing analyses (see section 4.2).

Considering the limitations of available diagnostic kits, novel genotypes could serve as source of EKC outbreaks and thereby facilitate the spread of infectious agents by impeding their timely containment. Taken together, besides the timely and accurate virus determination, careful clinical diagnosis is a prerequisite to prevent EKC outbreaks.

3. Transmission and epidemiology

In Japan, thousands of EKC cases occur annually, according to surveys of occurrence which collate reports from approximately 600 ophthalmic fixed points nationwide [16,44]. Peaks are typically seen in the 34th week, mainly towards the end of the summer season, but nosocomial infections occur even during winter. Similarly, EKC in Germany is reported more frequently during the warmer humid months [20,45]. The frequency of infections in other countries is less understood as only Japan and Germany implement surveillance measures for EKC [19,20].

The stable virion structure of adenoviral capsids facilitates the spread of nosocomial outbreaks by contact with fomites [46,47]. Infectious virions can be transmitted by medical staff by touching towels

contaminated with viral particles in clinics and nursing homes [15]. Therefore, disposal of contaminated materials from patients and proper hand washing by healthcare staff are highly recommended preventive practices. The sharing of eye drop bottles among patients should be avoided, as these bottles can also be contaminated with the virus [24,40]. Furthermore, sterilization of hospital instruments by proper methods is indispensable, such as by autoclaving and disinfection for 2 min with 60% ethanol + 10% isopropanol + 1% n-butanol, 5 min with 80% ethanol, 10% iodine, or other compounds effective against adenoviruses [46–48].

Failed containment of nosocomial infections results in the closure of health centers and even factories suspected of being the source, which can have serious medico-social economic impacts [7,15,17]. Adenoviral infections manifest as severe complications in immune-compromised patients, such as infants, transplant recipients, and AIDS patients [38]; therefore, latent, asymptomatic, chronic and opportunistic adenoviral infections are potential clinical risks and source of new outbreaks [21,46]. It is noteworthy that adaptive immunity against one adenoviral type conferred by a previous infection is ineffective against infections by types of other adenoviral species [49]. On the other hand, the immunity conferred by one type against types of the same species is more difficult to assess due to effects of intraspecies recombination events [50].

4. Adenovirus identification from EKC cases: history and emerging new types

4.1. History of circulating EKC-related adenoviruses

In 1954, HAdV-8 was isolated from an EKC case and identified as the previously undescribed pathogen behind “shipyard eye” disease, which was reported since 1889 in multiple outbreaks [10]. After 1969, AHC outbreaks were characterized as arising enterovirus infections [51,52], which prompted more rigorous surveillance of ocular infections. After 1973, EKC was also related to a variant of HAdV-19 reported in Europe and America as 19a [11]; however, closer inspections of strains mistyped as 19a demonstrated the existence of a third differentiable serotype involved with EKC outbreaks that was named thereafter as 37 [12].

4.2. New typing methods and nomenclature

Occasionally, identification of adenovirus in infections led to contradictory results in typing of strains by either serology or partial sequencing of the major epitope determinants, i.e., penton base, hexon and fiber (Fig. 2A–B) [53,54]. Subsequently, phylogenetic analyses of complete genome sequences were employed to resolve the genetic relatedness of the strains which supported a recombinant origin in many cases [3–6,50,55]. Therefore, new types are denominated as genotypes due to their genomic characterization, and they are referred to by the distinct recombination in the penton base, hexon, and fiber (PHF) open reading frames (ORFs) [43]. The genotype for each ORF is assigned as the closest reference genotype clustering in the respective phylogenetic tree (for example see Fig. 2C) [43].

Initially, type numbers were assigned based on serological analysis, leading to serotype numbering from 1 to 51 [9,56,57]. However, the advent of more affordable and rapid molecular typing methods revealed mistyped strains [6,58]. These strains have been progressively re-classified and demonstrated to be increasingly circulating and responsible for outbreaks since 2000 [19,59] (Fig. 1). Currently, more than 80 genotypes, including 51 serotypes, are classified into seven species, A to G, based on nucleotide and deduced amino acid sequences [60,61]. HAdV-D is the most type-diverse species in the genus with > 50 genotypes, including many with recombinant origins (Fig. 3A and Table 1) [50,62,63].

4.3. Emerging new HAdV types

4.3.1. Adenovirus 53 [P37H22F8]

The first report of EKC caused by HAdV-53 was in 2008 from a retrospective study of a Japanese outbreak that occurred in 2003 [5]. A comparison of partial nucleotide sequences derived from the hexon and fiber ORFs suggested a mosaic between types 22, 37, and 8 (Fig. 3 and Table 1). A similar report of EKC cases in 2005 from Germany involved strains serotyped as 22 [64], and subsequent phylogenetic analyses (Fig. 4A) led to the conclusion of a recombinant origin [65]. Notably, HAdV-22 was firstly isolated from an infant with trachoma [66]. A subsequent study compared the genomes of strains related to HAdV-53 isolated in 1987, 1989, and 1995 [2]. The recombination analysis provided evidence that the strains 53-like were intermediate recombinant genomes between types 22/37 and the currently circulating HAdV-53, which, in the latter case, evidenced a fiber ORF identical to HAdV-8 [2]. In another study, based on our clinical observations, infections by HAdV-53 seems to be more frequently related to milder infections without corneal inflammation than cases involving HAdV-8 and 37 (*manuscript in preparation*). The number of reported cases per year vary, but HAdV-53 remains a frequent cause of EKC in Asian countries [19].

4.3.2. Adenovirus 54 [P54H54F54]

HAdV-54 was first reported in 2000 from a nosocomial outbreak at a university teaching hospital in Japan. Initially, isolated strains were mistyped as HAdV-8 due to cross-reactivity in serological analyses [3]. The complete genome sequence analysis of these strains identified them as a novel genotype: HAdV-54 [3]. Despite a Greek group recently reporting a strain with a partial hexon similar to HAdV-54 [67], all characterized cases to date have been limited to Japanese EKC, whereas the related HAdV-8 has steadily decreased in reported frequency (Fig. 1) [19,57,68]. HAdV-54 clusters monophyletically with HAdV-8, which is associated to severe cases amongst the EKC-related types [1,10,66]. Although serological analysis showed some cross-reaction with antiserum against serotype 8, and less so with serotype 9 [3], comparisons of hexon proteins at the amino acid level confirmed high pairwise identities with these types. HAdV-8 and 54 possess > 95% similarity to each other along their entire genome sequences. However, ORFs for penton base and hexon show lowered similarities, < 95% and < 90%, respectively, which has been suggested as evidence of ancestral recombination events (Fig. 4B). The reason behind the lack of reports pertaining to HAdV-54 prior to 2000 is unclear.

4.3.3. Adenovirus 56 [P9H15F9]

HAdV-56 was initially reported from cases in France and Japan. The cases in France in 2009 corresponded with a neonatal respiratory fatality with subsequent conjunctivitis in the health care workers who cared for the child [55]. In contrast, the report in Japan corresponded with 11 EKC cases disseminated across the country in 2008 [4]. The recombination and serological analyses of the virus genome demonstrated a recombinant origin involving types 26, 15 or 29, and 9 (Fig. 4C). The frequency of EKC cases attributable to HAdV-56 has since been increasing across Japan [19]. Interestingly, adenoviral ocular infections by intermediate strains between types 15 and 9 were reported in Europe in 1968 and the USA between 1970–1980 [69,70], suggesting an earlier origin for HAdV-56 that passed undetected or was mistyped by serological approaches. Notably, HAdV-56 was identified as the cause of a large EKC outbreak in China in 2012 [59].

4.3.4. Adenovirus 64 [P22H19F37]

HAdV-19 was first reported in 1955 from a case of trachoma in Saudi Arabia [71]. A strain with a similar serotype, but a strikingly distinct restriction enzyme pattern, was isolated 20 years later from EKC cases [72]. Therefore, following the naming convention of that time, the serotype and a letter representing the distinctive enzyme

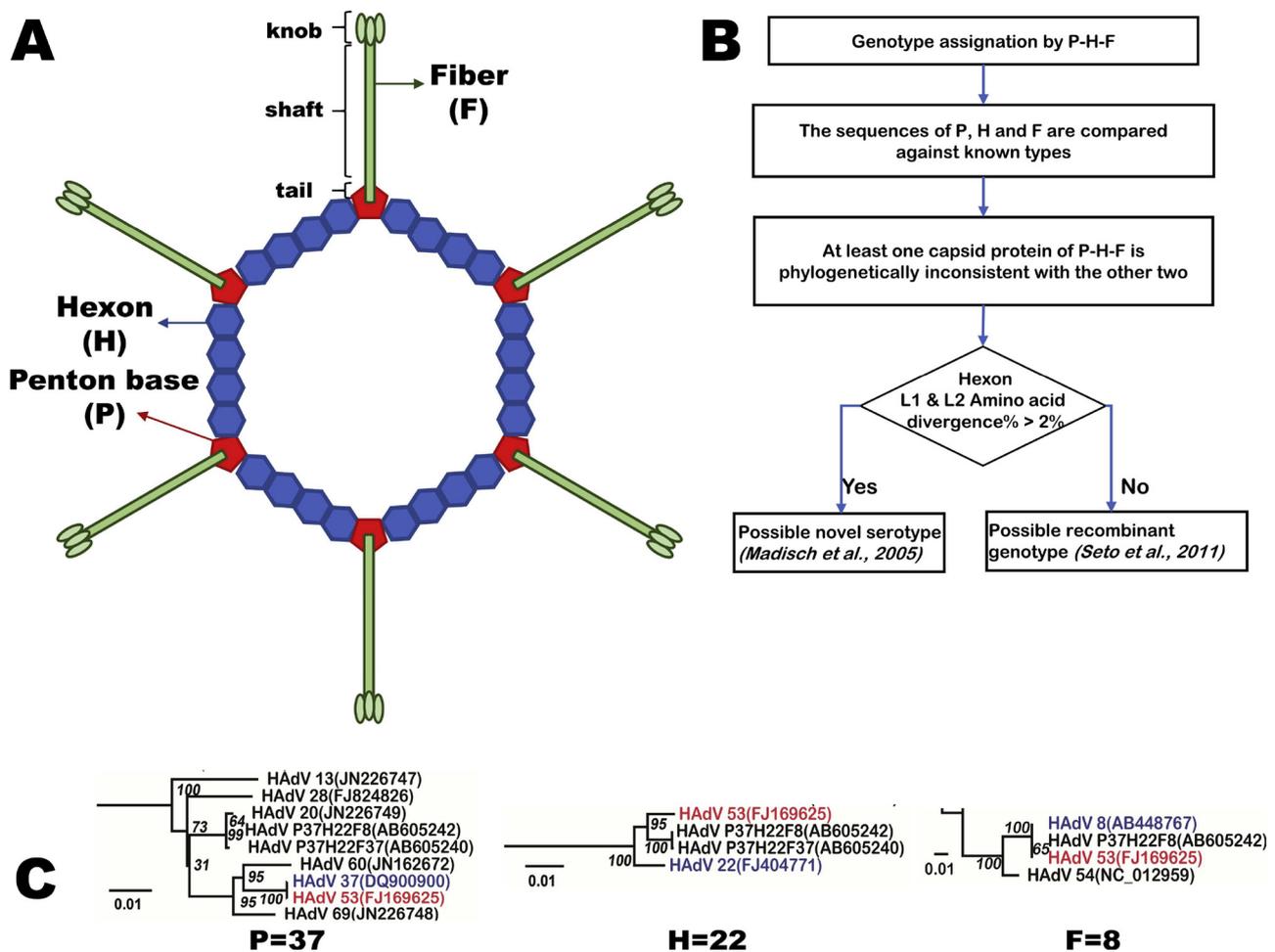


Fig. 2. PHF nomenclature diagram. (A) Schematic representation of the adenoviral major capsid proteins on the virion surface. (B) Flowchart for the assignment of novel genotypes. (C) Illustrative example of the closest types that are phylogenetically associated to type 53 in the penton base (P = 37), hexon (H = 22), and fiber (F = 8). Bootstrap support values are shown next to each branch.

restriction pattern were assigned to this strain: 19a. Recombination and phylogenetic analyses of each protein from HAdV-19a demonstrated that the penton base and hexon ORFs are recombinant regions with higher similarity to HAdV-22 and 19, respectively, than to HAdV-37, which is the putative origin of the genome backbone (Fig. 4D) [73]. The name HAdV-64 was assigned to the strain previously named ‘19a’ to recognize both the recombinant origin and its independence from HAdV-19 [6].

5. Uncovering unique properties of HAdV-D related to ocular infections

The fiber protein is an important determinant of tissue tropism [74], and possibly a factor limiting EKC to a subset of types that share phylogenetically related fiber proteins (Fig. 3D). The fiber knob has been suggested to be under positive selection [75], which favors amino acid compositions that bind cellular receptors in the ocular tissue. Fiber knobs of EKC-related types are predicted to have unusually high isoelectric points, enabling electrostatic interactions [76,77] to receptors, such as sialic acid-containing oligosaccharides [78–81]. Notably, E70 and CVA24v, which are associated with AHC, also bind to cells via sialic acid-containing glycans, supporting a link between receptors with sialic acid moieties and severe ocular diseases [82]. These observations have been used to the design of sialic acid analogs for topical treatment of EKC by blocking the initial attachment of fiber knobs in the adenoviral virions and facilitating their agglomeration and removal from the tissue [81,83,84].

Besides the genes encoding the major capsid proteins, other genomic recombination hotspots are important sources of genetic variation between types [50]. These hotspots localize in the E1, E3, and E4 transcriptional regions and encode proteins implicated in modulation of viral replication and the host immune response (Fig. 4) [85,86]. These regions have been shown to exhibit phylogenetic correlation, i.e. coevolution, despite being the target of frequent recombination events [62]. Furthermore, comparisons of phylogenetically related protein sequences in EKC- and non-EKC types have suggested fiber and proteins encoded in E3 as possible pathogenesis factors associated with the severity of EKC cases [62,75,87,88].

Systematic studies of the adenoviral E3 region subsequently revealed multifunctional proteins that target various host factors, effectively modulating diverse host processes. Notably, CR1 β , a 49 kDa protein uniquely expressed by HAdV-D, is secreted from infected cells to target other uninfected immune cells, such as natural killer (NK) cells, with immune-suppressing effects [88,89]. Among the human receptors identified as interacting with CR1 β , two striking groups include signal lymphocytic activation molecule (SLAM; CD150) family receptors and leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1) and 2 (LILRB2) inhibitory receptors expressed in immune cells [89], and variations in the binding proteins was observed between different types and cell lines [90]. CR1 β binds motifs present in CD45 isoforms expressed on leukocyte cell membranes [88]. EKC-related types putatively escape from conjunctiva NK cell immune responses by modulating the NK cell subpopulations and altering the expression of ligands for the activation of NK cell receptors in infected

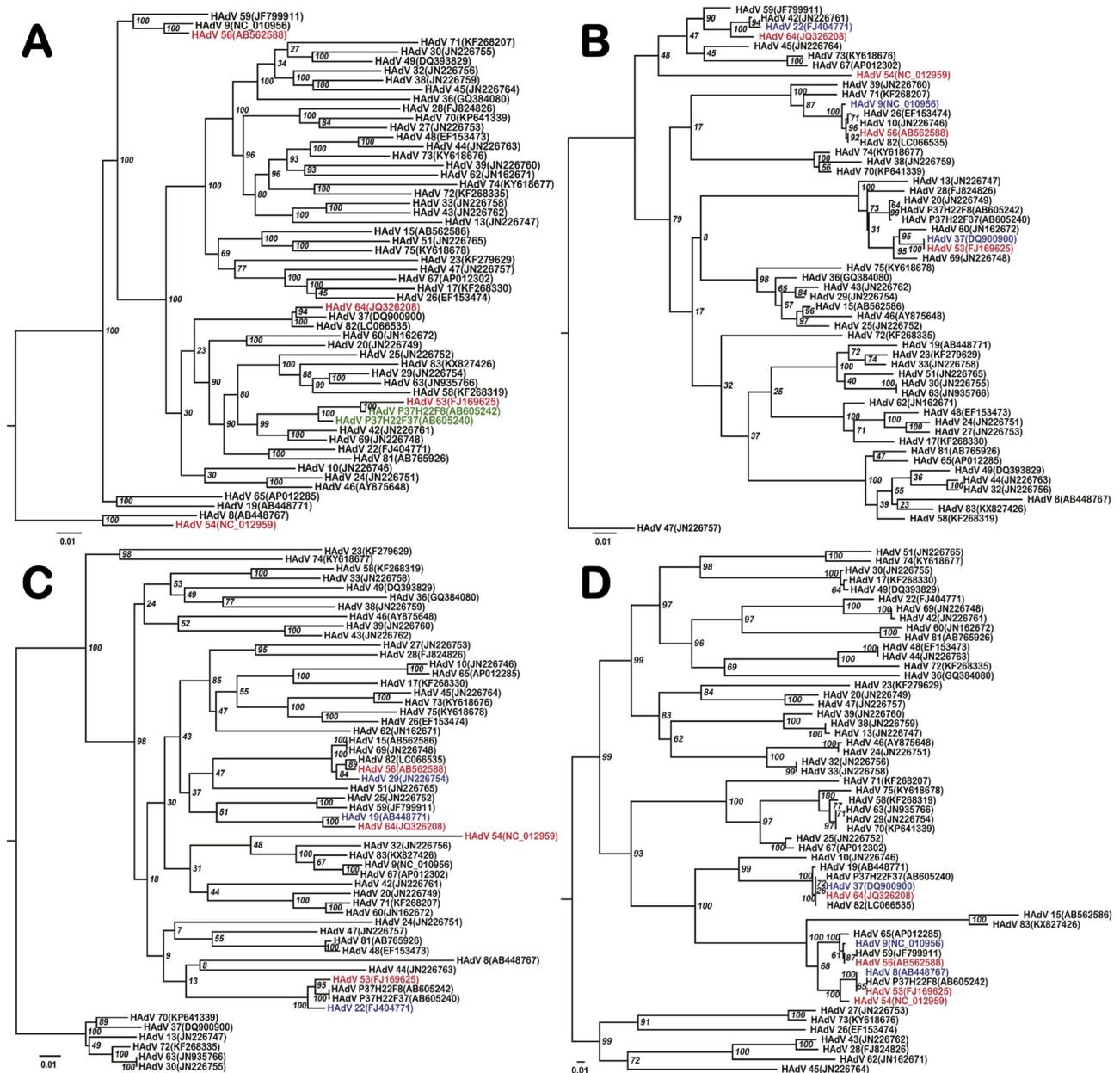


Fig. 3. Maximum likelihood inferred phylogenetic trees for human adenovirus D. The phylogenetic trees for human adenovirus D types using the whole genome (A) and the open reading frames for penton base (B), hexon (C), and fiber (D) were inferred with maximum likelihood approaches in RAxML using a general time-reversible evolutionary model allowing for invariant sites and heterogeneity among sites modeled with a gamma distribution (GTR + G + I). Bootstrap support for the branches is shown with 1000 repetitions. Novel types are highlighted in red and types clustering with the novel types are highlighted in blue. Types reported to be intermediary forms of type 53 are shown in green in (A). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

cells [91].

6. Challenges in understanding the pathogenesis of EKC and in development of therapeutics for EKC

In general, there is no specific antiviral treatment against adenovirus infections [92]. If inflammation or infiltration of the cornea is detected, eye drops with anti-inflammatory agents or corticosteroids are recommended; however, the latter should be restricted to complicated cases, as animal studies and a clinical trial showed the use of topical corticosteroids extend the duration of the infection despite alleviating the discomfort in patients [92–94]. Cases presenting MSI can be treated with topical 0.05% cyclosporine A or 0.03% tacrolimus to shorten the infection and clear the MSI [95,96]. A recent double

blinded clinical trial reported near complete recovery and absence of MSI on day 5 by treating the EKC infection four times a day with drops containing povidone-iodine 1.0% and dexamethasone 0.1% [92]. In EKC, pseudomembranous conjunctivitis can be mixed with streptococci infections that lead to corneal perforation; therefore, antibiotics should be applied prudently. Neonates are at risk of mixed infections with bacteria; therefore, antibacterial eye drops should be applied [20].

The interactions of virus and host innate immune system are suspected to play a role in the corneal infiltration developed only in a subset of patients infected with HAdV-D [91]. Identification of the mechanisms behind corneal infiltration and development of therapeutics have been hindered by the lack of proper animal models that recapitulate the immune conditions of the ocular tissue. Some alternatives have been suggested, each with distinct advantages and

Table 1
PHF classification of novel genotypes related to EKC.

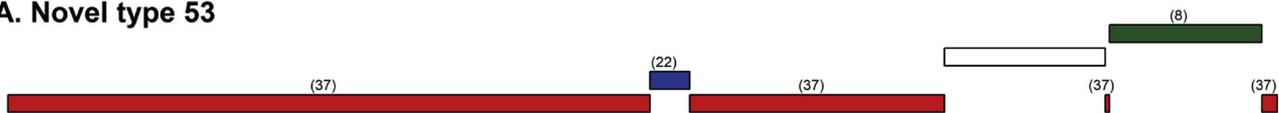
Genotype	Protein	Clustered type	Closest type ^a	Nucleotide identity (%) ^a	Bayesian posterior probability ^b	Percentage of bootstrap support ^c
53	penton base	37	37	100	1.00	100
	hexon	22	22	98	1.00	100
	fiber	8	8	100	1.00	100
54	penton base	54	45	94	–	48
	hexon	54	9	91	0.95	48
	fiber	8	8	97	1.00	100
56	penton base	9	9	99	1.00	100
	hexon	15	15	99	1.00	100
	fiber	9	9	99	0.87	61
64	penton base	22	22	98	1.00	100
	hexon	19	19	98	1.00	100
	fiber	37	37	100	1.00	100

^a Closest type identified by BLAST.

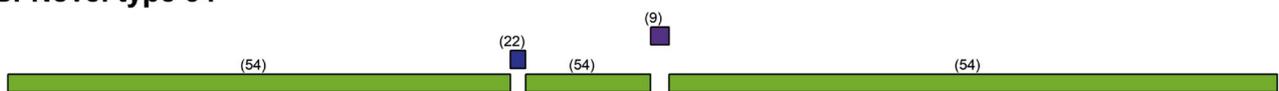
^b Posterior probability estimated by MrBayes v3.0 with 1 million states.

^c Percentage of bootstrap support estimated by RAXML v8.2.10 with 1000 repetitions.

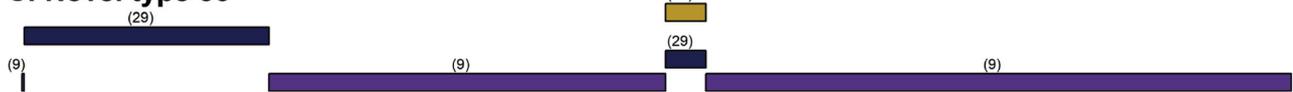
A. Novel type 53



B. Novel type 54



C. Novel type 56



D. Novel type 64

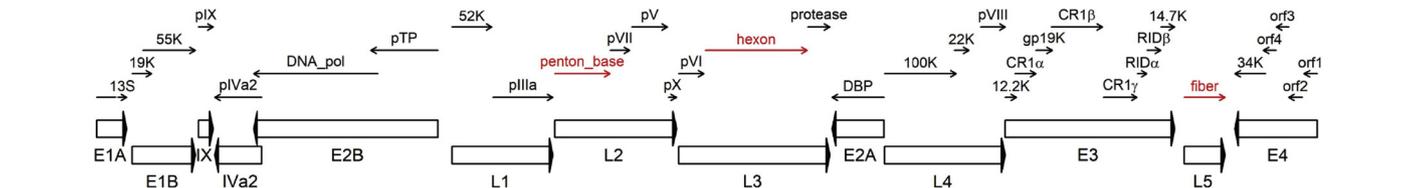
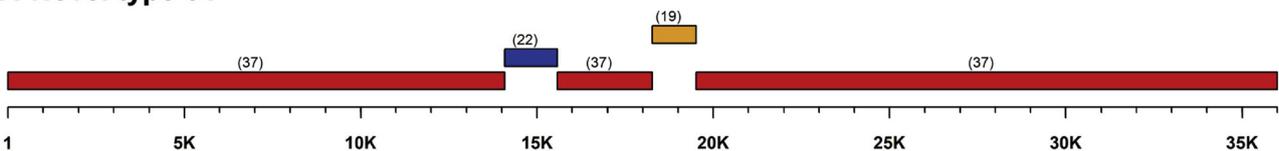


Fig. 4. Putative recombinant origins of genomic regions in novel types. Genomic distribution of recombined regions for novel types 53 (A), 54 (B), 56 (C), and 64 (D). The boundaries of the putatively recombined regions were determined by the recombination detection program (RDP). The putative recombinant parent of the recombined block is shown in parentheses. At the bottom of the diagram, the annotation of the human adenovirus D genome is shown as a reference. Positions shown are relative to the alignment and the encoding regions corresponding to penton base, hexon, and fiber (PHF) are highlighted in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

drawbacks. For example, the viral replication of HAdV-37 in a porcine cell culture system [97] and three-dimensional culture system with human cells [98] are *in vitro* systems that allow experimentation but lack the intricacies of the complete ocular tissue. On the other hand, using the mouse as an animal model, despite offering such anatomical complexity, has the drawback that human adenoviruses do not replicate

in the mouse cornea [99], as well as the intrinsic differences between the human and mouse immune systems, particularly at the level of innate immunity [100].

7. Conclusions

Timely diagnosis of EKC requires careful clinical observation and sensitive virus detection assays, which are not yet available in most clinics. Since effective therapeutics against EKC are also unavailable, the best clinical practice remains relying on implementation of prevention and containment measures following the timely reporting of newly detected outbreaks. New genotypes are potentially overlooked and may constitute sources for new EKC outbreaks. Recombination events among circulating HAdV types are a steady source of potentially emergent threats and subsequent spread in immunologically naïve populations. Therefore, proper identification of the new types is particularly important to control EKC outbreaks. More detailed characterization of the clinical features, genomic analysis of new types and the development of model systems are imperative to deepen our understanding of EKC and develop efficacious therapeutics.

Author contributions

G.G., N.Y., K.A. and N.K. equally contributed to the conceptualization, data curation, formal analysis and gather and review of references. G.G. wrote the original draft. N.Y., K.A. and N.K. reviewed and edited the text according to their clinical experience.

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Competing interests

None declared.

Ethical approval

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