The association of picornaviruses with gastroenteritis

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Many members of the family *Picornaviridae* survive passage through the stomach and some are known to replicate in the intestinal tract. Yet these picornaviruses are not considered as a leading cause of acute gastroenteritis. Further investigation of gastroenteritis cases not associated with viruses known to cause diarrhoea may serve to delineate further between picornaviruses causing gastroenteritis and an incidental finding.

Picornaviruses are non-enveloped, single-stranded, positive-sense RNA viruses (Figure 1) classified in the order *Picornavirales*, family *Picornaviridae*. The 12 picornavirus genera cause a wide range of diseases in both humans and animals: *Aphthovirus, Avihepatovirus, Cardiovirus, Enterovirus, Erbovirus, Hepatovirus, Kobuvirus, Parechovirus, Sapelovirus, Senecavirus, Teschovirus* and *Tremovirus* (Table 1)[1]. While adenoviruses, astroviruses, caliciviruses and rotaviruses are accepted as the main causal agents of viral gastroenteritis, a variety of picornaviruses is also routinely detected in faecal specimens. However, it can be difficult to prove a causal association between gastroenteritis of unknown aetiology and a family of viruses that are often transmitted by the faecal-oral route but result in asymptomatic infection.

Enteroviruses

Despite human enteroviruses deriving their name from one of their principal sites of replication as enteric viruses, any diarrhoeal symptoms are usually considered secondary to more major diseases resulting from spread to other organs via the bloodstream. The range of clinical presentation of enterovirus infection includes poliomyelitis, meningitis, encephalitis, myocarditis and hand, foot and mouth disease. A viral meningitis outbreak associated with echovirus types 6 and 9 in Western Australia reported gastrointestinal symptoms in 83% (55/66) of the echovirus 9 cases and 63% (37/59) of the echovirus 6 cases[2]. Diarrhoea and/or vomiting was reported in 10% (7/70) of the confirmed echovirus 6 and 9 infections with non-meningitis

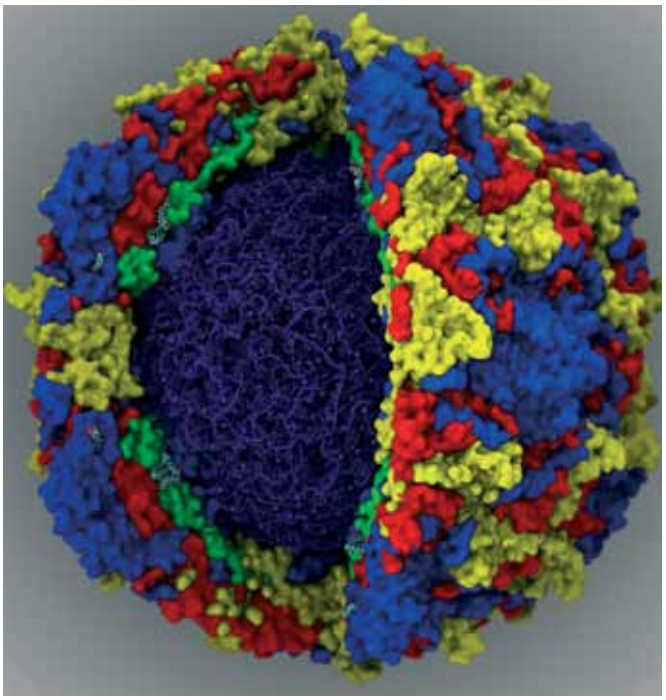

Figure 1. Computational model of the Mahoney strain of wild poliovirus type 1, family Picornaviridae, genus Enterovirus after molecular dynamics simulation. The non-enveloped virus capsid is composed of four structural proteins-VP1 (blue), VP2 (red), VP3 (yellow) and VP4 (green)-and associated lipids. The single stranded positive sense RNA genome (purple) is depicted within the capsid associated with ions.

illness. Enterovirus 71 is most commonly associated with hand, foot and mouth disease but cases with neurological involvement have been reported in many countries including Australia. While meningitis or encephalitis was reported as the primary diagnosis in 15 of 24 hospitalised patients with confirmed EV71 infection in Denmark, nine of the 15 patients had symptoms of diarrhoea and gastroenteritis was the main diagnosis for another four patients[3].

Human rhinoviruses are now classified in the genus *Enterovirus*[1]. A recent publication reported the detection of species C rhinovirus in faecal specimens from three patients with diarrhoea in the absence of respiratory symptoms[4]. Other pathogens – parechovirus, rotavirus and *Salmonella* group B – were detected individually from the three specimens so the role of species C rhinoviruses with gastroenteritis is unclear. Nevertheless, the detection of species C rhinovirus in faecal specimens warrants further investigation to determine whether they have an association with diseases other than respiratory infections.

Aichi virus

Aichi virus was initially isolated in 1989 from the prefecture of the same name in Japan. Sequencing the virus genome resulted in its classification as a member of the picornavirus genus *Kobuvirus*[1]. Aichi virus has been identified in 1–2% of sporadic cases of gastroenteritis worldwide and up to 20% of faecal specimens from outbreak cases in Japan, mainly associated with eating oysters[5]. However, a recent report from Germany provided evidence of an association between Aichi virus and acute diarrhoea via human-to-human transmission that did not involve food[6]. Bovine kobuvirus has been officially classified by the International Committee on Taxonomy of Viruses but has not been associated with gastroenteritis. In contrast, porcine kobuvirus has been associated with diarrhoea in South Korea and other countries[7] but its taxonomic classification remains unassigned[1].

Parechoviruses

Human parechovirus types 1 and 2 were initially classified as echovirus types 22 and 23, respectively, but were reclassified in the genus *Parechovirus* and now include types 1–16[1]. Parechovirus was detected in 16.3% of 1,824 faecal specimens from children screened by RT-PCR in the Netherlands from 2004 to 2008, without investigating a possible disease association[8]. While in Thailand parechovirus was detected in 14.6% of 82 faecal specimens from children with acute gastroenteritis that were negative for adenovirus, astrovirus, norovirus, rotavirus and sapovirus supporting an association with the disease[9].

Novel picornaviruses

In recent years, the screening of faecal specimens for novel viruses by nucleic acid-based methods has produced interesting results. A new picornavirus, human common stool-associated picornavirus or cosavirus, was identified from cases of acute flaccid paralysis (AFP) reported as negative for poliovirus (non-polio AFP) in Pakistan. The virus was determined to have a high prevalence in Pakistan but was only detected in one patient after extensive screening of faecal specimens referred for enteric bacteriology in the United Kingdom[10]. Three groups independently identified a new picornavirus that is related to Aichi virus: kobu-like virus associated with stool and sewage or klassevirus was detected in paediatric gastroenteritis faecal specimens from Australia and the USA and a sewage sample from Spain[11]; and from paediatric gastroenteritis specimens by a second group[12]; while the closely related stool Aichi-like virus or salivirus was identified from non-polio AFP cases from Nigeria[13]. These three picornaviruses remain unassigned by the International Committee on Taxonomy of Viruses (Table 1)[1].

The screening of gastroenteritis specimens that are negative for the known causal agents by recently developed techniques such as pyrosequencing[14] may identify other novel picornaviruses; however, epidemiological studies in a number of countries will be required to elucidate the extent of their involvement with gastroenteritis.

In summary, the large group of picornaviruses do have an association with gastroenteritis. Aichi virus, parechoviruses and certain species of enterovirus are reported to have strong associations with viral gastroenteritis. Further investigation of gastroenteritis involving the novel picornaviruses described in this article is required and it will be intriguing to determine whether species C rhinovirus could also have a role.

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Table 1. *Picornaviridae* genera and type species assigned by the International Committee on Taxonomy of Viruses[1].

Genus	Type Species
Aphthovirus	*Foot-and-mouth disease virus*
Avihepatovirus	*Duck hepatitis A virus*
Cardiovirus	*Encephalomyocarditis virus*
Enterovirus	*Human enterovirus C*
Erbovirus	*Equine rhinitis B virus*
Hepatovirus	*Hepatitis A virus*
Kobuvirus	*Aichi virus*
Parechovirus	*Human parechovirus*
Sapelovirus	*Porcine sapelovirus*
Senecavirus	*Seneca Valley virus*
Teschovirus	*Porcine teschovirus*
Tremovirus	*Avian encephalomyelitis virus*
Unassigned	Human cosavirus
	Human klassevirus or salivirus
	Porcine kobuvirus

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Biographies

Bruce Thorley is the Head of the Australian National Enterovirus Reference Laboratory, which is accredited by the World Health Organization as a Polio Regional Reference Laboratory and located at the Victorian Infectious Diseases Reference Laboratory. He is also the Chief Investigator for the national Acute Flaccid Paralysis Surveillance program that investigates polio-like illness in children. In recent years he has focused on broadening surveillance for poliovirus in Australia by establishing an Enterovirus Reference Laboratory Network and testing environmental samples from sentinel sites.

Jason Roberts is a Senior Medical Scientist at the Victorian Infectious Diseases Reference Laboratory with a background in molecular diagnostic assay development. He is a consultant virologist for the Australian Polio Expert Panel and acts a temporary advisor for the WHO Polio Laboratory Network. His research interests relate to neurotropic RNA viruses, in particular the characterisation and molecular modelling of enteroviruses. He is currently collaborating with RMIT University, the Victorian Partnership for Advanced Computing and the Victorian Life Sciences Computation Initiative to recreate 'in silico', novel enterovirus and poliovirus proteins to determine the mechanisms of specific mutations associated with neurovirulence.