NC STATE UNIVERSITY

Norovirus: Framing the "Big" Picture

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USDA
United States Department of Agriculture
National Institute of Food and Agriculture

NoroCORE
Food Virology
Collaborative for Outreach, Research & Education

Member of the Human Enteric Viruses

- "Functional" rather than taxonomic group
- Common features
- Many routes of transmission
  - Source of contamination human feces (perhaps vomitus)
  - Infection initiated in GI tract
  - Symptoms largely gastrointestinal in nature
  - Many transmission routes
    - Person-to-person
    - Drinking water
    - Fomites
    - Soil
    - Bathing water
    - FOODS

Table 1
Human and Animal viruses (potentially) related with food-borne outbreaks.

Viruses			*Evidence* [a]	Clinical features
Norovirus	NoV	(+)sRNA	yes	gastroenteritis
Hepatitis A virus	HAV	(+)sRNA	yes	enterically hepatitis
Rotavirus		dsRNA	yes	severe gastroenteritis (children)
Astrovirus	ASV	(+) RNA	yes	mild gastro-enteritis (children)
Adenovirus	Ad	dsRNA	possible [b]	respiratory, eye, gastroenteritis infections
Enterovirus	EV	(+)RNA	less common	respiratory, eye, central nervous infections
Hepatitis E virus	HEV	(+)RNA	yes	enterically hepatitis
Tickborne encephalitis	TBE	(+)sRNA	yes, less common	encephalitis via unpasteurized milk of TBE infected animals
Parvovirus		ssDNA	little evidence	gastroenteritis
Coronavirus		(+)sRNA	linked to sewage-(water)	respiratory and gastroenteritis infections
Torovirus		(+)sRNA	role unknown	gastroenteritis in humans?
Picobirna virus		(+)sRNA	role unknown	gastroenteritis in immunocompromised

[a] see also: Greening GE. Human and Animal viruses in food(including taxonomy of enteric viruses). In Viruses in Foods. *Ed.* S.M. Goyal. Springer Science+Business Media, LLC, New-York. Pg 5-42.
[b] no documented evidence for food-borne transmission or disease resulting from consumption of contaminated shellfish

From: Duizer and Koopmans, 2007

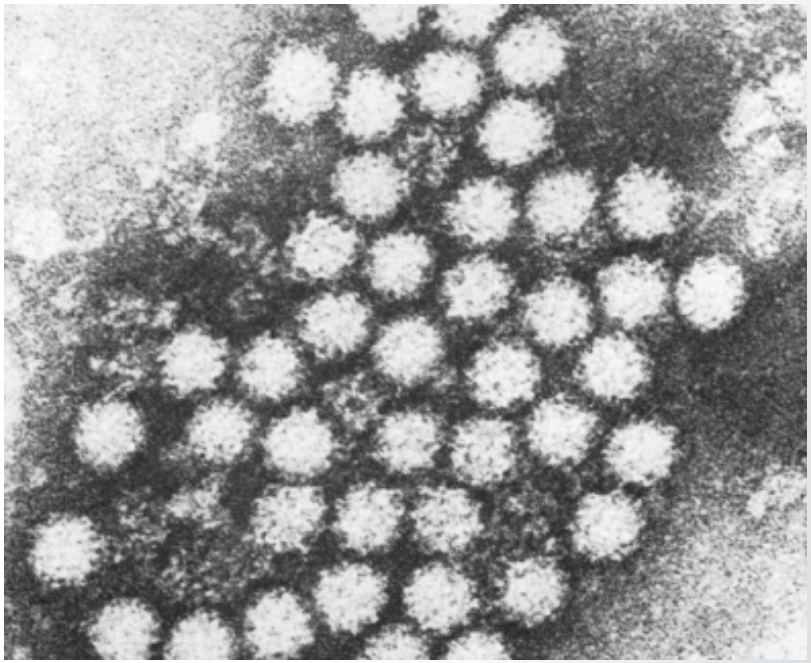
History of Foodborne Virus Emergence—Let's Not Repeat this One!

- "Infectious" hepatitis or "epidemic jaundice"
- In 1940's, recognized as an entity separate from "acquired" or blood-borne hepatitis
- Late 1950's to early 1960's, the Willowbrook studies
  - Mentally disabled children were fed fecal extracts from symptomatic patients
  - Developed classic hepatitis symptoms

Krugman, S., and collagues. Giles, J. P. and Hammond, J. (1967). Infectious hepatitis. *Journal of the American Medical Association,* **200,** 365.

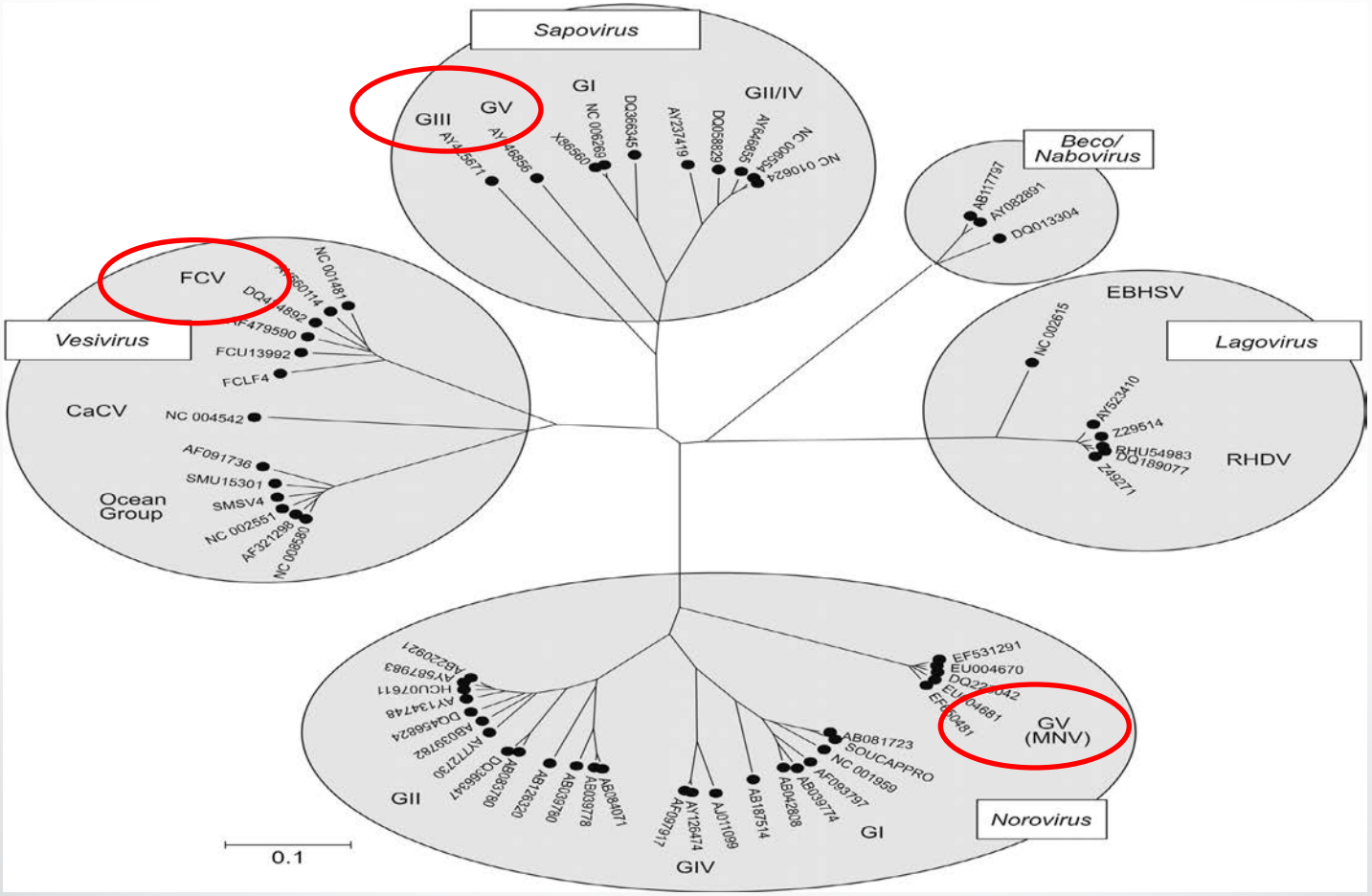
Discovery of the "Norwalk" Agent

- Human challenge studies (1940s and 1950s) sought to identify causative agent of "acute non-bacterial gastroenteritis"
- Electron microscopic examination stool specimen collected from 1971 outbreak in Norwalk, Ohio revealed presence of 27 nm particle
- Subsequent human challenge studies confirmed this as the infectious agent



Kapikian, A. Z., Wyatt, R. G., Dolin, R., *et al*. (1972). Visualization by immune electron microscopy of a 27 nm particle associated with acute infectious nonbacterial gastroenteritis. *Journal of Virology,* **10,** 1075-1081.

The *Caliciviridae* Family



The Norovirus Genus

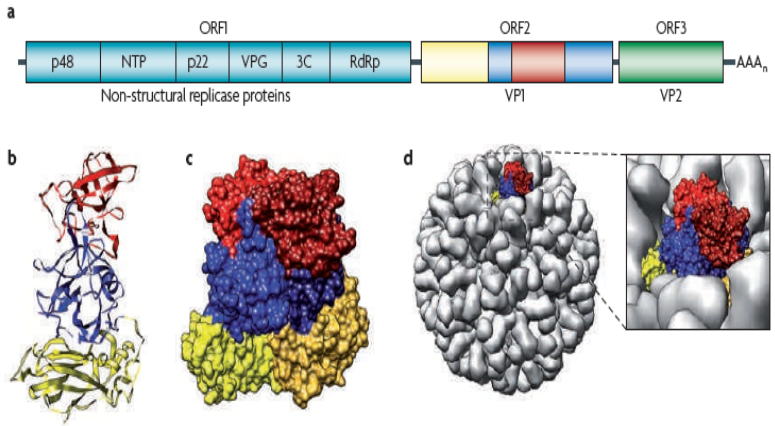
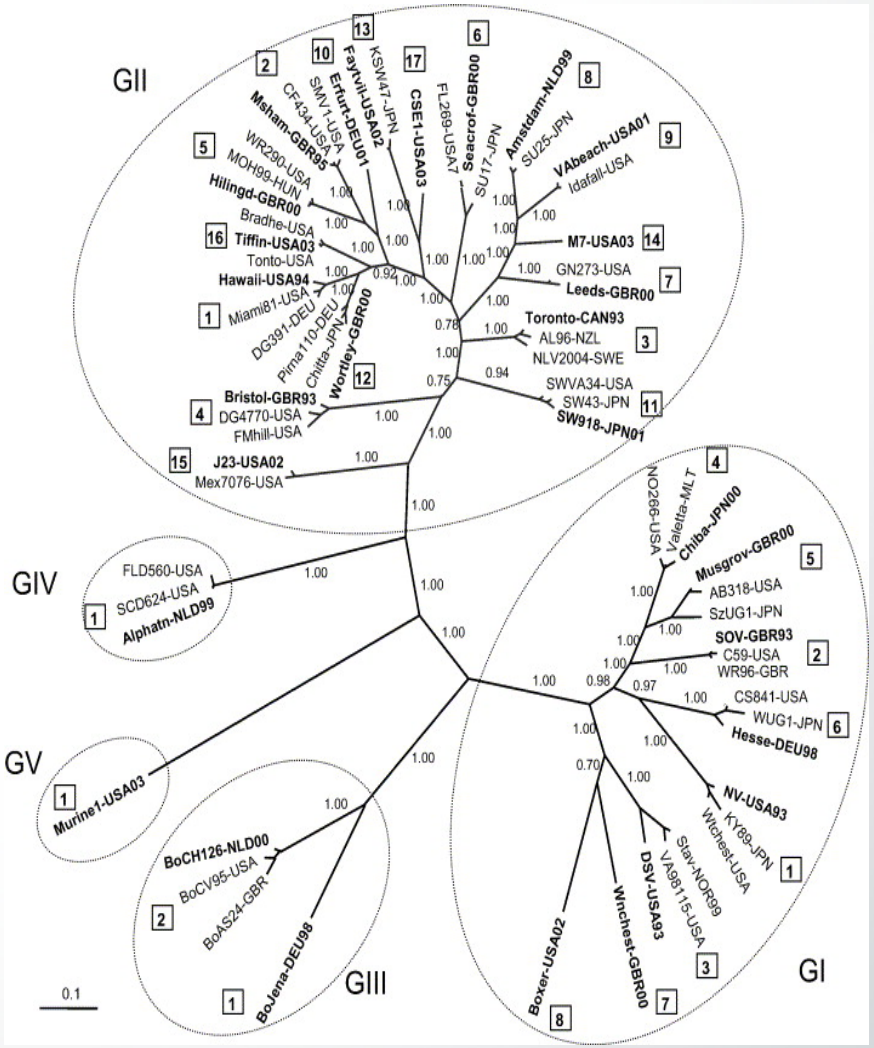


Figure 1 | **Genome organization and capsid structure. a** | The norovirus genome is composed of three open reading frames (ORFs). ORF1 (~5 kb) is located in the first two-thirds of the genome and encodes a ~200 kDa polyprotein that is auto-processed by a virally encoded 3C-like protease (3C) to yield the non-structural replicase proteins that are essential for viral replication[89]. The resultant proteins are: p48, an amino-terminal protein of unknown function (~48 kDa); nucleoside triphosphatase (NTP), a 2C-like protein; p22, a 22 kDa 3A-like protein; viral genome-linked protein (VPG), a protein that is covalently linked to the 5′ end of the genome; and RNA-directed RNA polymerase (RdRp), a 3D-like protein. ORF2 is 1.8kb in length and encodes the 57 kDa major structural capsid protein, viral protein 1 (VP1). VP1 is divided into two domains, the shell domain (yellow) and the protruding domain, which is further divided into two subdomains known as P1 (blue) and P2 (red). ORF3 is ~0.6 kb in length and encodes a 22 kDa minor basic structural protein, VP2 (REF. 89). **b** | The structure of the VP1 monomer is shown, with protein domains coloured as for part **a**. **c** | Two capsid protein monomers form the A–B dimer (indicated with the A monomer in lighter shades and the B monomer in darker shades), which allows the P2 domain to protrude from the viral particle. **d** | The virus-like particle is formed of 180 monomers of the capsid protein that assemble through different dimers. The A–B dimer, shown in colour, extends away from the capsid and provides the receptor-binding region and the sites of antigenic variation. In the virus particle, VP2 is incorporated in low copy number. Structural models were generated and pictures were rendered using MacPyMOL (Delano Scientific LLC, Palo Alto, California, USA).

From: Donaldson et al., 2010



From Zheng, 2005

The Smoking Gun: Epidemiological Significance

Food-Related Illness and Death in the United States

Paul S. Mead, Laurence Slutsker, Vance Dietz, Linda F. McCaig, Joseph S. Bresee, Craig Shapiro, Patricia M. Griffin, and Robert V. Tauxe
Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Foodborne Illness Acquired in the United States—Major Pathogens

Elaine Scallan,[1] Robert M. Hoekstra, Frederick J. Angulo, Robert V. Tauxe, Marc-Alain Widdowson, Sharon L. Roy, Jeffery L. Jones, and Patricia M. Griffin

- Leading cause of acute viral gastroenteritis worldwide
- Leading cause of food borne disease (~50%)
  - Hospitalization rate 0.03, 14,663 (8,097-23,323) annually [26%, 2nd in rank]
  - 149 (84-237) deaths annually [11%, 4th in rank]
- May be a significant cause of FBD of unknown etiology?

The Challenges

- Methodology
- Control
- Capacity