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Canine Noroviruses

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KEYWORDS

• Norovirus • Calicivirus • Dogs • Enteritis

Noroviruses (NoVs) were first identified in humans in 1972 on immune electron microscopy observation of the stools of volunteers infected with filtrates of faecal samples collected from a nonbacterial gastroenteritis outbreak occurred in 1968 in Norwalk, Ohio, USA.¹ Nonenveloped, small, rounded viruses (SRVs), 27 nm in size, were observed in the fecal filtrates and specific antibodies were detected in both experimentally and naturally infected individuals, suggesting that the particles were the etiologic agent of Norwalk gastroenteritis.

On genetic characterization, NoVs have been classified as a distinct genus of the Caliciviridae family.² NoVs have been now recognized as the major etiologic agent of nonbacterial acute gastroenteritis worldwide and they are estimated to cause more than 1 million hospitalizations and up to 200,000 deaths in children younger than 5 years on an annual basis.³ NoVs have been also identified in cows, pigs, mice, and carnivores, and the role of some animal species as potential source of novel human NoVs via interspecies transmission and eventually recombination has been hypothesized.⁴

ETIOLOGY

Caliciviruses are nonenveloped SRVs with a single-stranded, positive-sense, polyadenylated RNA genome of 7 to 8.5 kb.⁵ Based on their genetic relationships and genome organization, caliciviruses have been classified into 4 genera: namely *Vesivirus*, *Lagovirus*, *Sapovirus*, and *Norovirus*.⁵ More recently, other caliciviruses have been discovered and proposed as members of distinct genera: Nebraska-like viruses⁶ (*Nebovirus*) in cows, rhesus caliciviruses,⁷ Saint Valerienè-like viruses in swine,⁸ and avian caliciviruses.⁹ Caliciviruses have been associated to a variety of clinical signs, ranging from gastroenteric disease to exanthematic lesions, to severe systemic diseases and hemorrhagic forms, and they are recognized as important pathogens in both humans and animals.

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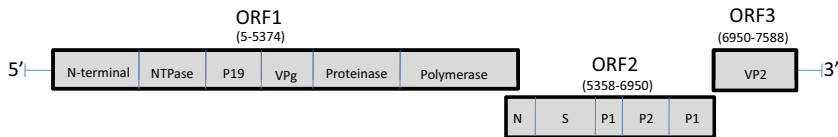


Fig. 1. Norovirus (strain Norwalk, accession M87661) genome organization. Proteolytic cleavage map of the non-structural polyprotein encoded by ORF1. The NH₂-terminal portion (N) of the highly conserved shell (S) domain and the protruding region (P) subdomains (P1 and P2) are also indicated.¹⁵

NoVs are important human enteric pathogens³ and they have also been detected in the stools of livestock animals, although their role as pathogens in these animals remains controversial.^{10,11} In mice, NoV is able to invade the central nervous system (CNS) in *STAT1*-deficient animals, causing fatal disease.¹² Mouse NoV has also been adapted to in vitro growth, thus providing an excellent model/surrogate for the study of human NoVs, which are noncultivable.^{13,14}

NoV genome is 7.5 to 7.7 kb in length and contains 3 distinct open reading frames (ORFs).⁵ ORF1 encodes a large polyprotein that is post-translationally cleaved into 6 nonstructural proteins, including the RNA-dependent RNA polymerase (RdRp). ORF2 encodes the capsid protein VP1, while ORF3 encodes a small basic protein, VP2 (**Fig. 1**).⁵ The viral capsid contains 180 copies of VP1 protein and a few copies of VP2. The VP1 contains 2 main domains, S and P. The S (shell) domain is highly conserved and connected through the P1 subdomain to the highly variable P2 (protruding) subdomain.^{15,16} The P2 region possesses several motifs that control binding to the host cell and virus antigenicity.^{17,18}

NoVs are genetically and antigenically highly heterogeneous. Accumulation of punctate mutations and recombination drive their evolution, generating an impressive diversity. The highly conserved ORF1/ORF2 junction region is a preferential site for NoV recombination.¹⁹ Recombination may create chimeric viruses with intermediate genetic features between the parental viruses, generating inconsistencies in the classification/nomenclature. A consistent and reliable classification of NoVs is based on the analysis of the complete capsid gene.²⁰ Strains within the same genotype (or cluster) share greater than 85% amino acid identity, while strains of different genotypes within the same genogroup share 55% to 85% amino acid identity.²⁰ Humans NoVs belong to genogroups (G) I, II, and IV.⁴ In addition, NoVs classified as GI have been detected in pigs,^{21,22} and GI/II NoVs in large and small ruminants.^{23,24} NoVs proposed as GV have been detected in mice.¹²

CALICIVIRUSES IN DOGS

Unlike calicivirus infections in cats,²⁵ canine caliciviruses are not regarded as important pathogens and they are not usually included in diagnostic algorithms for canine infectious diseases. Calicivirus-like particles have been occasionally identified by electron microscopy in specimens from dogs with fluid diarrhea and, in some instances, glossitis, balanitis, or vesicular vaginitis. Most isolates were feline caliciviruses (FCVs) and were likely acquired from cats.^{26–30}

Thus far, there are only 2 documented reports on the identification of authentic canine caliciviruses in dogs. In 1985 a calicivirus was isolated from the feces of a 4-year-old dog with bloody diarrhea and central nervous system disturbance in Tennessee, USA. The virus was found to replicate in experimentally infected dogs and

to elicit seroconversion, although disease was not reproduced. Also, the virus was antigenically unrelated to FCV and antibodies against the virus were identified in 76% of the canine sera collected.³¹ However, it was not characterized molecularly and its taxonomic status remains uncertain. In 1990, another calicivirus was identified in Japan in a 2-month-old pup with intermittent watery diarrhea.³² The virus, strain 48, was found to be antigenically and genetically unrelated to FCV and was tentatively proposed as a “true” canine calicivirus (CaCV) and included in the *Vesivirus* genus.^{33,34} Antibodies to CaCV 48 have been detected in 57% of dogs in Japan³⁵ and in 36.5% of dogs in Korea.³⁶

NOROVIRUSES IN DOGS

The first evidence of NoV in carnivores was documented in 2006 in a captive lion cub that died of severe hemorrhagic enteritis at 4 weeks of age in Pistoia, Italy.³⁷ The animal tested negative to all potential lion viral pathogens, and on bacteriologic investigations it was found to be infected by toxigenic *Clostridia*. Unexpectedly, NoV RNA was detected in the intestinal tract and, on genomic characterization, the virus was found to resemble human GIV NoVs (Alphatron-like), with 69.3% to 70.1% amino acid identity in the full-length capsid protein, and it was proposed as a distinct NoV genotype, GIV.2, while human Alphatron-like NoVs are GIV.1. Human GIV.1 NoVs are usually identified only sporadically in the human population, although they may be commonly detected in sewage samples from treatment plants,^{38,39} indicating that there are open gaps in the understanding of their ecology and in the diagnosis.

As lions are susceptible to the majority of canine and feline pathogens, the detection of NoV in lions raised the question of whether domestic carnivores represented the source of infection for the captive lion cub. By expressing in baculovirus the capsid protein of the lion NoV, virus-like particles (VLPs) were produced and used to set up an ELISA, revealing specific antibodies in 16.1% of feline and 4.8% of canine sera.⁴⁰ Also, by screening a collection of stools from dogs with gastroenteritis in Italy in 2007, NoV was detected in 2.2% (4 of 183) of the pups.^{41,42} The age of the pups ranged between 60 and 70 days and 3 of 4 pups were also co-infected by canine parvovirus. These direct and indirect pieces of evidence confirmed that domestic carnivores might harbor NoVs.

Shortly after the first identification, additional evidence about the circulation of NoVs in dogs has been documented. During an epidemiologic study in 2008 in Greece, a cluster of NoV infection was identified in a kennel in Thessaloniki in 6 pups, 2.5 to 3 months old, that were housed together,⁴³ suggesting the highly infectious nature of canine NoVs for young pups. All the NoV-infected animals were also co-infected by canine coronavirus.

In a 1-year survey in Portugal in 2008 of dogs from municipal shelters, veterinary clinics, and pet shops, NoV was detected in the stools of 25 of 63 (40%) of dogs with diarrhea and 4 (9%) of 42 asymptomatic animals. In most cases, the NoV-infected dogs displayed mixed infections by either canine parvovirus or coronavirus or both.⁴⁴

Also, NoV RNA was detected in 3 of 106 stools collected from pups with parvovirus gastroenteritis in 2007 in the United Kingdom (Martella and colleagues, unpublished information, 2011). These findings indicate the canine NoVs circulate in several European countries.

GENETIC HETEROGENEITY IN CANINE NoVs

Thus far, 6 canine NoV strains have been analyzed molecularly. Sequence information has been gathered on the RdRp region, at the 3' end of ORF1, the full-length capsid

protein (ORF2), and the minor basic protein (ORF3). The prototype canine NoV strain, Bari/170/07/ITA,⁴¹ resembles the virus lion NoV Pistoia/387/06/ITA, as the 2 viruses share 96.7% amino acid identity in the RdRp and 90.1% amino acid identity in the capsid protein. Likewise, the Greek strain Thessaloniki/30/2008/GRC resembles the canine virus Bari/170/07/ITA, both in the RdRp (100% amino acid identity) and the capsid gene (99.4% amino acid identity).⁴³

A large insertion of 20 residues can be observed in the P2 hypervariable domain of GIV.2 animal NoVs with respect to GIV.1 human viruses. By homology modeling and 3-dimensional alignment, the P insertion appears to form a loop protruding from the compact barrel-like structure of the P2 subdomain and exposed on the outer surface of the capsid.

Interestingly, another canine NoV strain, Bari/91/07/ITA, although sharing the same pol (RdRp) type as strains Dog/Bari/170/07/ITA and Lion/Pistoia/387/06/ITA, possesses a novel ORF2 gene, with the highest identity (57.8% amino acid) to the unclassified human strain Chiba/040502/04/JAP. This canine virus is distantly related (36.0%–54.5% amino acid identity) to all other NoVs,⁴² suggesting the existence in dogs of NoVs with a novel capsid genotype. The UK strain FD210/07/GBR resembles both in the RdRp (98.5% amino acid identity) and the capsid (95.0% amino acid identity) canine virus Bari/91/07/ITA.

The Portuguese NoV strain Viseu/C33/08/PRT and the UK strain FD53/07/GBR display a third capsid genotype. These viruses are related to each other (99.5% amino acid identity in the RdRp and 98.6% amino acid in the VP1), while they have only 63.1% to 63.9% amino acid identity in the full-length VP1 to the strain Bari/91/07/ITA and FD210/07/GBR (Fig. 2, Table 1).

PATHOGENIC POTENTIAL OF CANINE NoVs

The pathogenicity of canine NoVs in experimental infections in gnotobiotic or specific-pathogen-free (SPF) animals has not been assessed. Viral shedding could be monitored in a naturally infected pup with mixed infection by NoV and canine parvovirus type-2. The pup recovered from the disease 4 days after hospitalization but NoV was shed at detectable levels for 3 weeks.⁴¹ Prolonged NoV shedding after infection/disease has been documented for weeks or even months in human patients.^{45,46} Likewise, murine NoV shedding can last for several weeks in immune-competent mice,^{12,47} and this has been interpreted as a mechanism of virus persistence in the host population.

In most cases, NoV-infected dogs were also co-infected by other pathogens. That mixed infections can elicit mechanisms of synergism, as observed between coronaviruses and parvoviruses,^{48,49} cannot be ruled out. Interestingly, the frequency of detection of NoV has been found to differ significantly between symptomatic and asymptomatic dogs in a 1-year survey in Portugal.⁴⁴ Interpretation of these findings is not clear, as several factors can influence the course of NoV infection. As canine NoVs appear to display a number of capsid genotypes, there could be differences in the biological properties (eg, virulence, ability to bind to canine cellular receptors, and so on) among the various NoV strains. In addition, mechanisms of genetic resistance could alter the outcome of NoV infection in some canine breeds, thus confounding the picture. Experimental human infection studies with the prototype Norwalk virus (GI.1) showed that the study participants were repeatedly susceptible or resistant to symptomatic infection following repeated virus challenge.⁵⁰ Subsequent studies have revealed that human NoVs recognize histoblood group antigens (HBGAs) as receptors or co-receptors. HBGAs are complex carbohydrates present on the surface of red blood cells and mucosal epithelia, or free in biological fluids such as milk and

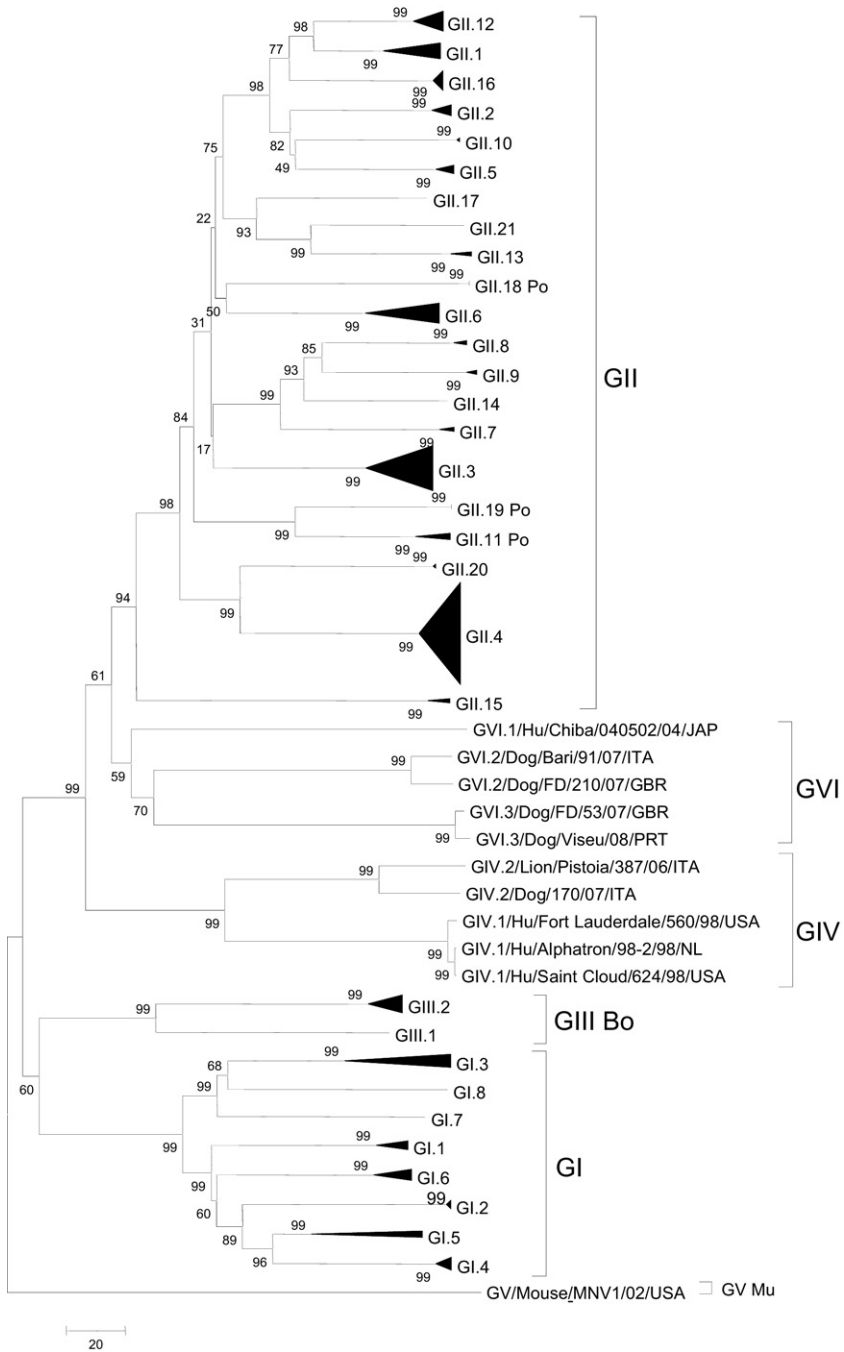


Fig. 2. Phylogenetic tree constructed on the full-length amino acid sequence of the capsid protein. The tree was constructed using a selection of NoV strains representative of the genogroups I to V. bo, bovine; po, porcine; mu, murine; hu, human.

Table 1

Classification of canine NoVs based on the full-length capsid protein VP1

Genogroup	GI	GII	GIII	GIV		GV	GVI			Classification	
				GIV.1	GIV.2		GVI.1	GVI.2	GVI.3	ORF1	ORF2
Lion/Pistoia/387/06/ITA	41,6-37,8	49,7-45,8	36,6-36,5	69,2-68,9	90,1	36,9	50,0	54,4-54,5	54,1-53,8	GIV.2	GIV.2
Dog/Bari/170/07/ITA	41,1-36,9	50,2-45,9	35,9-35,1	68,0-67,7	90,1	36,6	50,0	54,3-54,0	53,8-53,4	GIV.2	GIV.2
Dog/Bari/91/07/ITA	40,8-38,0	54,4-50,2	37,7-37,0	54,4-54,2	54,5-54,4	36,0	57,8	95	63,8-63,2	GIV.2	GVI.2
Dog/FD/210/07/GBR	40,7-38,1	54,7-50,4	37,6-37,1	53,4-53,3	54,6-54,1	36,4	57,5	95	63,9-63,1	GIV.2	GVI.2
Dog/FD/53/07-2/GBR	41,5-38,4	53,4-48,8	39,6-38,1	53,7-53,5	54,1-53,8	36,7	55,2	63,9-63,8	98,6	GIV.2	GVI.3
Dog/C33-Viseu/07/PRT	41,2-38,1	53,9-48,6	39,3-37,8	53,4-53,2	53,8-53,4	36,4	54,9	63,2-63,1	98,6	GIV.2	GVI.3

saliva. HGBAs are synthesized under the control of highly polymorphic ABO, Lewis, and secretor gene families. Different NoV genotypes variously recognize these antigens, and the recognition patterns have been found to correlate with susceptibility to infection and illness.^{51–54} The global spread and predominance of pandemic GII.4 NoV variants have been related to the broad range of recognized HBGA types.⁵¹ Similar mechanisms appear to influence genetic resistance of pigs to NoV infection under experimental conditions.⁵⁵

DIAGNOSIS

Several sets of primers have been designed for molecular diagnosis of human NoVs in different diagnostic regions (A–C) spanning the ORF1 and ORF2.⁵⁶ Diagnostic tools can be greatly affected by NoV genetic diversity.⁵⁷ In most cases, diagnosis of canine NoV was accomplished using broadly reactive primers sets targeting diagnostic region A within the RdRp, such as p289-p290 or JV12Y/YV13I.^{58,59} However, it has been shown that designing more specific primers can allow increasing significantly the detection rates of canine NoVs (from 1.9% to 27.6%).⁶⁰

Several unsuccessful attempts have been made to adapt to *in vitro* cultivation the prototype canine NoV strain Bari/170/07/ITA, using both canine and feline cell lines and primary cells. With the exception of murine NoVs,¹³ NoVs appear to be noncultivable *in vitro*.^{14,61} Replication of human NoVs *in vitro* has been demonstrated in a 3-dimensional organoid model of human small intestinal epithelium, displaying a high level of cellular differentiation.⁶² However, these results have not been reproduced in other laboratories.

An ELISA has been set up using the baculovirus-expressed capsid protein of the GIV.2 lion NoV.⁴⁰ This assay was successfully used to assess exposure of domestic carnivores to NoVs. However, considering the extent of the genetic heterogeneity of canine NoVs, generating synthetic antigens based on other capsid genotypes (GVI.2 and GVI.3) would be necessary to portray a more precise picture.

ZOONOTIC POTENTIAL OF CANINE NoVs

Dogs are regarded as vectors of viral, bacterial, or parasitic zoonosis,⁶³ but the risks linked to transmission of enteric viruses are almost ignored. However, several pieces of evidences indicate that enteric viruses may have a zoonotic potential: (1) infection of young children by rotavirus strains of canine and feline origin has been documented repeatedly⁶⁴; (2) having dogs in or near a home has been recognized as a risk factor for acquisition of IgA antibodies specific for NoV in infants in a seroepidemiologic study conducted in rural Mexico⁶⁵; and (3) a calicivirus gastroenteritis outbreak occurred in a nursing home in Exeter, UK, in 1983 and was found to be epidemiologically linked to the household dog. Acute gastroenteric disease in the dog occurred 24 hours before the human index case and antibodies specific for the human caliciviruses were identified in the dog, thus suggesting a possible association.⁶⁶ (4) Also, under experimental conditions, NoVs have been found to be able to cross the host species barriers. A GII.4 human NoV was able to infect and induce diarrhea in gnotobiotic piglets and calves,^{11,10} thus indicating that heterologous infections can occur. (5) In addition, NoV strains genetically similar to the canine virus Bari/91/07/ITA (88.9% nucleotides and 98.9% amino acid identities in a short fragment spanning the 5' end of ORF2) have been detected in oysters destined for raw consumption in Japan (strains Yamaguchi/C34/03/JAP, Yamaguchi/24B/02/JAP, and Yamaguchi/24C/02/JAP⁶⁷). This could indicate that canine-like GVI NoVs are common in some geographic settings and that they can contaminate the coastal areas and accumulate at

detectable levels in bivalve molluscs destined for raw consumption. Contamination of shellfish by animal (porcine and bovine) enteric caliciviruses, alone or in conjunction with human viruses, has been demonstrated in 22% of oysters in United States.⁶⁸ However, while the impact of sewage pollution on the water environment by livestock may be relevant, especially in the areas of high livestock production, it is difficult to explain the presence of canine-like NoVs in oysters. A possible explanation for this is that similar viruses are harbored in other animal species or in settled human populations. (6) Finally, human GIV (Alphatron-like) NoVs are genetically much more related to animal GIV NoVs (GIV.2) than to GI and GII human NoVs, suggesting points of intersection during their evolution. The modalities of this intersection are uncertain but likely they were favored by the strict social interactions between humans and pets.

SUMMARY

NoV are regarded as emerging pathogens in humans, and the creation of worldwide surveillance networks has allowed the researchers to gather important epidemiologic information and to gain unforeseen insights into the mechanisms of NoV evolution. The discovery of NoVs in carnivores and the genetic relationship between them and some human viruses raise interesting questions inherent in the ecology of these viruses and the possibilities of interspecies transmission. Also, it will be interesting to assess whether and to which extent NoVs impact on pet health.

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