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Review

Bovine noroviruses: A missing component of calf diarrhoea diagnosis

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ABSTRACT

Noroviruses are RNA viruses that belong to the Genus *Norovirus*, Family *Caliciviridae*, and infect human beings and several animal species, including cattle. Bovine norovirus infections have been detected in cattle of a range of different ages throughout the world. Currently there is no suitable cell culture system for these viruses and information on their pathogenesis is limited. Molecular and serological tests have been developed, but are complicated by the high genetic and antigenic diversity of bovine noroviruses. Bovine noroviruses can be detected frequently in faecal samples of diarrhoeic calves, either alone or in association with other common enteric pathogens, suggesting a role for these viruses in the aetiology of calf enteritis.

Introduction

Morbidity and mortality due to calf diarrhoea are responsible for substantial economic losses in the cattle industry throughout the world (Virtala et al., 1996). Noroviruses (NoVs) are RNA viruses that belong to the Genus *Norovirus*, Family *Caliciviridae*, and have emerged as important causes of acute, non-bacterial, food and waterborne gastroenteritis in human beings worldwide (Patel et al., 2009). The prototype NoV, Norwalk virus, was first described by Kapikian et al. (1972). Through the use of electron microscopy (EM), viruses with typical calicivirus morphology have been identified in faecal samples of domestic animals (Scipioni et al., 2008b), including in faecal samples from diarrhoeic calves (Woode and Bridger, 1978).

The first bovine enteric caliciviruses (BoCVs), morphologically indistinguishable from human noroviruses (HuNoVs), were described in cattle in England (Bo/Newbury2/76/UK virus; Woode and Bridger, 1978) and Germany (Bo/Jena/80/DE virus; Günther et al., 1984; Günther and Otto, 1987). Subsequently, bovine noroviruses (BoNoVs) have been identified in America (Smiley et al., 2003; Wise et al., 2004), Africa (Hassine-Zaafrane et al., 2012) and Asia (Park et al., 2007). BoNoVs may play a role in the aetiology of calf enteritis (Scipioni et al., 2008b), but are not included in routine diagnostic algorithms for calf enteric diseases and their impact on livestock production remains unclear. The aim of this review is to describe these poorly known bovine enteric pathogens, to discuss their pathogenesis, to summarise available techniques for their diagnosis and to report their current molecular epidemiological features.

Genome organisation and molecular virology of noroviruses

The *Caliciviridae* family includes five genera (*Norovirus*, *Sapovirus*, *Lagovirus*, *Vesivirus* and *Nebovirus*) (Green, 2013), along with incompletely characterised, unassigned caliciviruses (Farkas et al., 2008; L'Homme et al., 2009; Carstens, 2010) (Fig. 1). The BoNoV genome is a single-stranded, positive sense, polyadenylated, 7.3–7.5 kbase RNA molecule (Liu et al., 1999; Oliver et al., 2007a). In the HuNoV genome, the 5′ end of the genomic RNA is covalently linked to the genome-linked viral protein (VPg) (Jiang et al., 1993). The untranslated regions (UTRs) at the 5′ end of all NoV genomes are typically 5–78 nucleotides (Green, 2013).

NoV genomes are organised into three open reading frames (ORFs), with the exception of murine norovirus (MuNoV), which has a fourth ORF (ORF4) (McFadden et al., 2011) (Fig. 2). Starting from the 5′ end of the genome, ORF1 encodes the viral non-structural proteins, ORF2 encodes the major capsid protein (VP1), and ORF3 encodes the minor structural protein (VP2). In the MuNoV genome, ORF4 produces virulence factor 1 (VF1), which regulates the innate immune response (McFadden et al., 2011).

Open reading frame 1 is translated as a large polyprotein of 1740 amino acids (aa), which is cleaved by the viral protease (3CLPro) to encode six mature non-structural (NS) proteins (Thorne and Goodfellow, 2014). The coding sequences for the N-terminal non-structural protein NS1-2 (p48), NS3 nucleotide triphosphatase (NTPase)/RNA helicase, NS4 protein (p22), NS5 protein (VPg), NS6 protease (3CLPro) and NS7 RNA-dependent RNA-polymerase (RdRp) are transcribed from the 5′ end to the 3′ end of ORF1, respectively.

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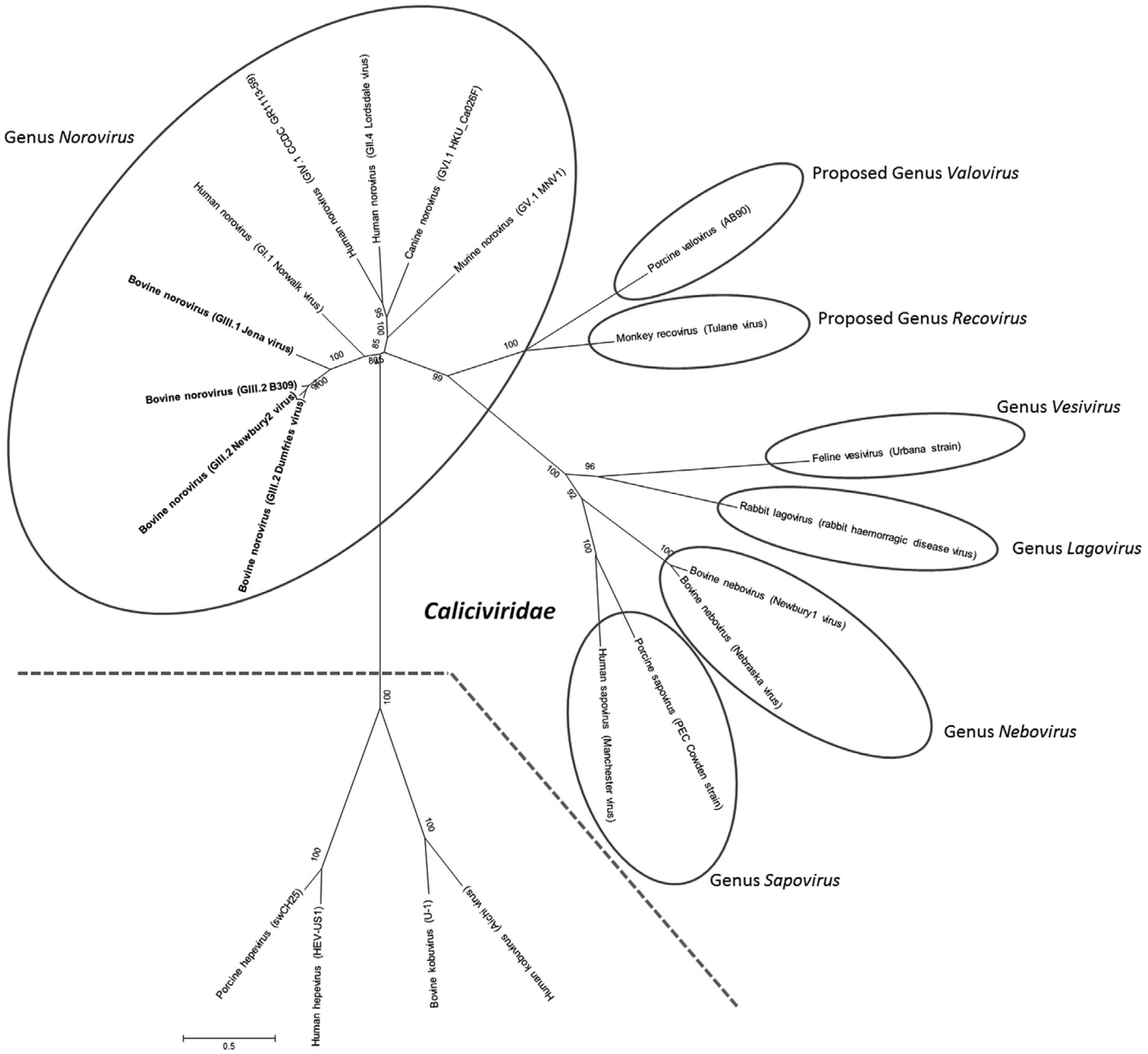

Fig. 1. Phylogenetic relationships between different human and animal, positive sense, single stranded RNA viruses, including bovine noroviruses highlighted in bold face in the tree. The tree was inferred with the maximum likelihood method on complete genomic sequences from representative viruses (see Appendix: Supplementary Table S1 for GenBank accession numbers), with 1000 bootstraps and the General Time Reversible + γ substitution model (Tamura et al., 2013).

ORF2 is translated as a 55–60 kDa protein, VP1, which is involved in self-assembly and capsid formation, receptor recognition, host specificity, strain antigenic diversity and immunogenicity (Chen et al., 2004). X-ray crystallographic structure studies using Norwalk virus-like particles (VLPs) showed that VP1 contains two major domains, a well-conserved shell (S) domain, which forms the core of the particle, and a more variable protruding (P) domain, which extends away from the central core (Prasad, 1999). The P domain is further divided into the P1 and the highly variable P2 subdomains (Fig. 3); the latter is involved in interaction with the host cell membrane (Tan et al., 2004; Tan and Jiang, 2014) and possesses the most important epitopes (Lindesmith et al., 2013). VP2 most likely is involved in capsid assembly and genome encapsidation (Vongpunsawad et al., 2013).

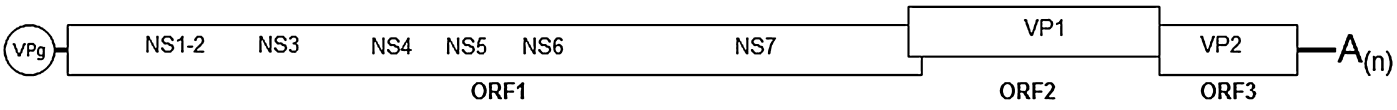

Fig. 2. Representative genomic organisation of the bovine norovirus genome.