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Genetic evolution of *Canine Coronaviruses*

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Introduction

Canine coronavirus (CCoV), a member of the *Alphacoronavirus* genus of the *Coronaviridae family*, is an enveloped, positive-sense, single-strand RNA virus (Pratelli, 2011). CCoV was first described during an epizootic in a canine military unit in Germany in 1971 (Binn et al., 1974), and starting from this report, the virus was isolated repeatedly from affected dogs. Today CCoV appears to be enzootic worldwide, and dogs of all breeds and ages seem to be susceptible to infection (Bandai et al., 1999; Escutenaire et al., 2007; Godsall et al., 2010; Naylor et al., 2001; Soma et al., 2011; Stavisky et al., 2010; Yeşilbağ et al., 2004). CCoV is generally responsible for mild gastroenteritis, though it may be more severe in young pups, or in combination with other pathogens. Common signs include soft faeces or fluid diarrhoea, vomiting, dehydration, loss of appetite and, occasionally, death. Dual infections by CCoV and Canine Parvovirus type 2 (CPV2) are especially severe when they occur simultaneously, but CCoV can also enhance the severity of a sequential CPV2 infection (Pratelli et al., 1999). Although fatal infections are sporadic, CCoV is an important pathogen responsible for epizootics (Pratelli, 2006), and interestingly, in the last two decades researchers focusing on the genomic variability of CCoV strains, have identified new genotypes/types (Pratelli, 2011).

After preliminary observation on the genetic variability of the M protein (Pratelli et al., 2002), extensive sequence analysis of the viral genome, provided strong evidence for the existence of two separate genetic clusters of CCoV, assuming that *coronaviruses* in carnivores possess a sort of "dynamic" genome (Pratelli et al., 2003b). The nt sequence of a region encompassing about 80% of the S gene of the strain Elmo/02, clearly indicates that a novel CCoV type, closely related to Feline Coronavirus type I (FCoV type 1), circulates among dogs.

Elmo/02 was designated as the prototype of the newly recognised genotype 1, CCoV type 1, and the reference strains were designated as CCoV type 2 (Pratelli et al., 2003a). On the basis of the genetic relatedness to Transmissible Gastroenteritis Virus (TGEV) of swine, CCoV type 2 has been classified into two subgenotypes, CCoV tipe 2a and CCoVtype 2b (Decaro and Buonavoglia, 2008). Phylogenetic analysis of the S gene clearly demonstrates that CCoV type 1, strain Elmo/02, segregates with FCoVs type 1 rather than CCoV type 2 and FCoV type 2. Moreover, the presence of the stretch of basic residues RRXRR was indicative of a potential cleavage of the S protein. A similar basic motif is present, approximately in the same position, in all *betacoronaviruses* and *gammacoronaviruses* identified and classified to date (Pratelli, 2011). An accessory gene, ORF3, 207 aa long, unique to CCoV type 1, was identified. Interestingly, no transmembrane region was detected suggesting that the protein is secreted from the infected cells (Lorusso et al., 2008). Both genotypes are largely distributed worldwide. CCoVs were found in Western European dog populations (Decaro et al., 2009a), and in all European countries examined (Stavisky et al., 2010; Escutenaire et al., 2007). Reports of widespread CCoVs have come from Australia (Benetka et al., 2006), China (Wang et al., 2006) and Japan where the detection rate for dogs aged under 1 year was 66.3%, with a simultaneous detection rate of both types up to 40% (Soma et al. 2011).

In 2001, a novel CCoV, strain UWSMN, was identified from a fatal case of gastroenteritis in pups in Australia (Naylor et al., 2001). Sequence analysis of fragments of the S and polymerase genes revealed 21 unique sites and 112 sites, randomly interspersed, where the strain was different from at least one of the other strains analyzed. These observations suggested that UWSMN-1 was generally divergent due to a gradual accumulation of mutations throughout its genome, which may be reflective of its isolated evolution in Australia (Naylor et al., 2002).

Recently, a CCoV type 2a pantropic variant, strain CB/05, was associated with systemicfatal disease in young dogs (Buonavoglia et al., 2006). An experimental study demonstrated that the new virus was able both to infect CCoV seropositive dogs and to induce clinical signs irrespective of the viral dose administered in the challenged dogs (Decaro et al., 2010). This observation poses an important question on the efficacy of CCoV vaccines currently employed.

CCoVs with a potential double-recombinant origin through partial S-gene exchange with TGEV were identified in the gastrointestinal tract and internal organs of pups died with acute gastroenteritis (Decaro et al., 2009). The virus was strictly related to TGEV in the N-terminal domain of the S protein, whereas the rest of the genome revealed a higher genetic relatedness to CCoV type 2. As already noted, this new virus could prejudice prophylaxis programs, as dogs administered classical CCoV vaccines may be susceptible to infection caused by the recombinant virus.

Another example of the evolution of dog coronaviruses as a consequence of the accumulation of point mutations, small insertions and deletions in coding and noncoding regions of the genome, was the identification of a Respiratory Canine Coronavirus, CRCoV. The virus showed a close relationship to the *betacoronavirus* in the polymerase and S genes, and was distantly related to enteric CCoVs. Since its detection in 2003, CRCoV was found in dogs in several European countries, as well as in Canada and in Japan (Decaro et al., 2007; Ellis et al., 2005; Kaneshima et al., 2006; Priestnall et al., 2006; Priestnall et al., 2007; Yachi and Mochizuki, 2006).

All these observations raise questions regarding the biology of CCoVs. Although in recent years new data have shed light on obscure aspects of the infection, new studies are to extend and complete knowledge on these viruses, in terms of both prophylaxis and virus evolution.One of RNA's most intriguing features is its ability to carry genetic information despite its labile nature. Genetic recombination is an important mechanism for generating novel genomes that may have selective advantages over parental genomes. Although nonsegmented RNA viruses generally exhibit undetectable recombination frequencies, the recombinations for the entire coronaviruses genome were calculated to be as high as 25% (Baric et al., 1990). The high frequency of RNA recombination is probably the result of the unique mechanism of coronavirus synthesis, which involves discontinuous transcription and polymerase jumping. It is possible that the viral polymerase associated with the incomplete nascent RNAs, dissociates from its template at a random point and switches to a homologous site on a different RNA template to complete RNA synthesis by a copy-choice mechanism. Depending on the precision of the repair mechanism, the repaired genome may be similar to the parental genome, or it may contain further mutations (Lai, 1992).

As a consequence, the RNA viruses have the potential to rapidly adjust to certain negative pressures. These events clarify the evolutionary processes leading to the proliferation of new virus strains, serotypes and subtype, as happened for SARS-CoV and for new CCoVs. Notwithstanding the several studies carried out on CCoVs, there are a lot of aspects yet to be clarified: the meaning of simultaneous infection by CCoV type 1 and CCoV type 2, the real pathogenetic role of these two viruses, the immune response against CCoV type 1 and CCoV type 2, and the assessment of CCoV type 2-CB/05-like virus distribution among dog populations.

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