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Review Article

How to Update the Number of Canine Distemper Virus Genotypes Based on Official Genbank® Data?

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Abstract

The Canine Distemper Virus (CDV) is the causative agent of a complex infection present in a wide range of hosts. It is a pathogen that affects various orders of species, including primates, cetaceans, and various families of carnivores. It should be noted that the virus can be transmitted to wildlife, including aquatic carnivores, through contact with domestic canids. This route of transmission is increasingly common, due to the fact that domestic species invade the habitat of wild species, which facilitates contact between them.

The clinical diagnosis of the disease is complex due to the wide range of signs present, which requires confirmation by means of laboratory tests. The reference test is the Reverse Transcription Polymerase Chain Reaction (RT-PCR), with which the viral strains have also been characterized based on the analysis of the H gene, which is the most variable. Thanks to RT-PCR, the presence of at least 14 circulating VDC lineages in various hosts around the world has been determined, of which two have been described in Chile, these being the America-1 and Europe-1/South America- lineages. 1.

In the present work, all the available sequences of the VDC H gene available in the Genbank® will be reviewed with the intention of verifying, through the construction of a phylogenetic tree, the appearance of new lineages or if the situation remains as described by Ke and collaborators in 2015. Undoubtedly, the results will provide information on the origins, evolution and spatiotemporal distribution of the virus.

Keywords: Genotypes, CDV, H Gene, Evolution, Immune response

Introduction

Canine Distemper Virus

Canine Distemper (CD) also known by the names of "canine distemper", "hard pad" or Carré's disease is a disease with worldwide distribution caused by the Canine Distemper Virus (VDC), belonging to the *Mononegavirales* order, *Paramyxoviridae* family and Morbillivirus genus [1]. VDC mainly affects canids and other families of carnivores, such as felines, viverrids (civets, genets), mustelids (otter, ferrets) and procyonids (raccoons, coatis). However, the spectrum of VDC has broadened in recent years, and cases related to this agent have been observed in other species, such as pinnipeds and phocids [2,3].

Genome and Structure of the Virion

The CDV has a single-stranded, negative-sense, unsegmented RNA genome that is about 15,700 nucleotides in length. It contains six genes that code for virion proteins. The nucleocapsid (N gene, 1.5 kb) is the protein responsible for the protection of viral RNA. The matrix protein (M gene, 1 kb) plays relevant roles in virion morphology and assembly. Large polymerase (L gene, 6.5 kb), and phosphoprotein (P gene, 1.5 kb) are the proteins that form a functional polymerase complex and are responsible for viral RNA replication. F, 1.9 kb), is a glycoprotein that is essential for mediating fusion between the viral particle and the host cell membrane, providing the virus with the necessary mechanism to pass from one

cell to another. Hemagglutinin (H gene, 1.8 kb) is the glycoprotein responsible for viral adhesion to the host cell [4,5].

The CDV P gene is a highly conserved gene of the virus [6] and, as in other viruses belonging to the family *Paramyxoviridae*, it is polycistronic, encoding three different proteins P, V and C [7-9]. The P protein is essential for viral replication, is synthesized in excess in infected cells, and shows a high turnover rate, presenting transient functions during nucleocapsid assembly and RNA synthesis. On the other hand, proteins C and V are not considered essential for replication. The P protein linked to L integrates the polymerase complex responsible for RNA synthesis (transcription and replication) [8,10].

Pathogenesis and Pathology

The pantropic nature of the virus stands out, arising from various tissues of the host to such an extent that it is suspected as the first pre-diagnosis in susceptible canids with multisystem disease. The latter is because VDC is transported by macrophages and other cells of the immune system, via blood (viremia) and/or lymphatics. Among the main evident signs, it is possible to mention: In the respiratory system; cough, serous or mucopurulent rhinitis/conjunctivitis due to secondary bacterial contamination. In digestive system; diarrhea, vomiting. In nervous tissue; seizures, cerebellar syndrome (mobility and coordination conditions), paralysis, muscle spasms of nervous origin, among others [11].

Diagnosis (Clinical, Serological, Viral Isolation, Molecular Techniques)

The diversity of signs makes diagnostic research difficult. This added to techniques such as Immunohistochemistry and ELISA that do not satisfy the sensitivity, specificity, and speed. Molecular methods based on Polymerase Chain Reaction (PCR) preceded by Retro Transcription (RT) of genomic RNA, provide a diagnosis of high sensitivity, high specificity, and speed [3].

Polymerase Chain Reaction (PCR)

The PCR technique was developed in the 1980s, and since then it has revolutionized molecular genetics, making it possible to study a wide range of genes. It has been used in multiple areas where the enormous potential of PCR to amplify minute amounts of DNA (or RNA) has been particularly attractive [4]. Recently, it has been successfully applied for nucleic acid detection, as it is a highly specific, rapid and sensitive method for antemortem diagnosis of CDV infection in dogs, regardless of CDV presentation, humoral immune response, and distribution of the virus [12-14]. Generally, for the detection of CDV by RT-PCR, conserved regions within the viral genome are used as the main targets for amplification, such as the nucleocapsid protein gene (N gene) [12,14].

Thus, the RT-PCR technique has allowed the study of viral genetic variations, through the molecular characterization of the H gene sequence of the genome, currently describing at least 14 circulating lineages of VDC: Africa-1; Africa-2; America-1; America-2; Asia-1; Asia-2; Asia-3; Asia-4; Europe-1/South America-1; Europa-2 (Wild European); Europe-3 (Arctic); like Rockborn; South America-2; South America-3 [15].

Genetic Characterization in South America

In Argentina, the first report on the characterization of circulating DCV strains in South America was restricted. These studies evidenced the co-circulation in that country of two genetic variants or genotypes. In the other works, H gene fragments were further analyzed by restriction fragment length polymorphism (RFLP) and sequencing. A single Nde I site (restriction site) was detected in all 24 wild-type strains, but was absent in the vaccine strains [16,17]. In the State of Paraná in Brazil, it will be prolonged that the circulating CDV strains are closely related to those of the Europa 1 lineage of DCV, with marked differences with respect to other recognized geographical groups of CDV isolates and vaccine strains. VDC strains from this region of southern Brazil appear to be related to those from Europe 1 [18]. Two co-circulating lineages with different prevalences are detected in Uruguay: the Europe 1 lineage and a new South America 2 lineage. The Europe 1 lineage was the most prevalent in South America. They suggested changing the name to Europe 1/South America 1 lineage. The South America 2 lineage was found only in Argentina and was related to wild-type strains of CDV [19].

In Ecuador, a new VDC lineage was described based on the analysis of the Fsp region of South American strains, named Sudamerica-3 (SA3) [19], while in Colombia the studies carried out described a distinct monophyletic group, clearly separated from previously identified wild-type and vaccine lineages and proposed naming this lineage as “South America-3” [20]. In our country, at least two lineages have been described, corresponding to the America-1 and Europe-1/South America-1 lineages [21]. Finally, in Peru, the existence of a new lineage in South America was reported, which includes strains from Peru, Ecuador and North America called NA4/SA3 [17].

Evolutionary History

CDV, along with Rinderpest and Measles, are ‘mass disease’ morbilliviruses and most likely arose after the development of agriculture, when the large, dense, and interacting human-animal populations needed to maintain the viruses as endemic infections [22]. CD was described based on its clinical signs from cases in South America and Europe dating from the 17th century, until finally in 1905, when Henri Carré was able to isolate the virus [23]. The first complete sequence of the VDC H gene dates from 1975

in the United States. Since then, the number of reported sequences has increased, leading to the fact that there are currently more than 400 sequences in the GenBank database.

The development of molecular methodologies, the implementation of phylogenetic analysis, and the advancement of new computational techniques allow today to study in more detail the phylogenetic relationships of circulating strains [17]. Obtaining data about ancestry relationships between circulating strains, migration routes, or substitution rates (substitutions per site per year) is part of the information that can be obtained through coalescence studies. Thus, in 2015, an analysis was carried out using 208 H gene sequences belonging to 16 countries from samples collected between 1975 and 2011. In this study, it was estimated that the current circulating strains most likely originate from North America. This ancestor would have diversified: the one currently called North America-1), while the second expanded, giving rise to the rest of the lineages that currently circulate worldwide [24]. Subsequent phylodynamic analyses supporting these results, contributing to the knowledge of the evolution and spatiotemporal distribution of the virus [17, 24, 25].

Although these results indicate the United States as the place of origin of VDC, they do not refute the historical records of the 18th century, since the data used cover separate samples from the year 1975. The time restriction described, in addition to the wide range of hosts that it has, the VDC generates the need to have a significantly more representative majority of the entire existing viral population. The latter to reduce bias in the inferences that are made.

Materials and Methods

This work can be done in any Virology and Microbiology laboratory in any third world country.

Controls and Samples

As controls, all the nucleotide sequences of the H gene previously described [25] will be used in order to verify the existence of the genotypes described by the aforementioned author: Africa-1; Africa-2; America-1; America-2; Asia-1; Asia-2; Asia-3; Asia-4; Europe-1/South America-1; Europa-2 (Wild European); Europe-3 (Arctic); like Rockborn; South America-2; South America-3. The new samples will consist of the remaining H gene sequences available in the Genbank® dating after 2016. Both the control samples and the control samples plus the new samples will be analyzed using the MEGA program to develop the respective phylogenetic tree, considering the same previous characteristics [25]. Equipment to used: for the analysis through the MEGA program, a mobile computer, DELL i5, 2.4 Mhz, 500Mb is adjusted.

Discussion

What has been proposed can allow us to corroborate the existence of new CDV genotypes around our planet or find ourselves with the surprise that no others have been described in recent years. Who cares? It is a recurring question in several academics dedicated to the study of other pathogens that emerge in our human species. We must not forget that according to André Lwoff, “viruses are viruses” and there are probably no differences between those that affect animals and those that affect us (CDV and Measles for example).

Conclusion

Today we have biotools that must be used and, therefore, we will have no excuse for carrying out scientific research of an acceptable level.

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Conflict of Interest

Authors declare no conflict of interest.

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