



Peer Community In Infections

Wild canine viruses in the news. Better understanding multi-host transmission by adopting a disease ecology species community-based approach

Jean-Francois Guégan  based on peer reviews by **Arvind Varsani** and 1 anonymous reviewer

Marta Canuti, Abigail V.L. King, Giovanni Franzo, H. Dean Cluff, Lars E. Larsen, Heather Fenton, Suzanne C. Dufour, Andrew S. Lang (2024) Diverse fox circovirus (*Circovirus canine*) variants circulate at high prevalence in grey wolves (*Canis lupus*) from the Northwest Territories, Canada. bioRxiv, ver. 2, peer-reviewed and recommended by Peer Community in Infections. <https://doi.org/10.1101/2024.03.08.584028>

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According to the international animal health authority, i.e., the World Organization on Animal Health (WOAH, former OIE), circoviruses are part of the Circoviridae family, which only includes 2 genera Circovirus and Cyclovirus, and infect swine, canine, ursid, viverrid, felid, pinniped, herpestid, mustelid, and several avian species (WOAH 2021). They are small (12–27 nm), non-enveloped, circular, single-stranded DNA viruses, viral replication is nuclear, and wild and domestic birds and mammals could serve as natural hosts. If most infections caused by circoviruses are subclinical in both wild and domestic species, they can be responsible for severe diseases in the commercial pig industry due to the Porcine circovirus-2 (PCV-2). These viruses can constitute a threat to wildlife, and cause their hosts to become immunocompromised, and animals often present with secondary coinfections.

Canine circoviruses (CanineCV) harbour a worldwide distribution in dogs, and is the sole member of the viral genus to infect canines. They can be detected in wild carnivores, such as wolves, badgers, foxes and jackals, which indicates an ability for cross-species transmission between wildlife and domestic dogs. However, fox circovirus (FoCV), a distinct lineage of CanineCV, has been identified exclusively in wild canids (foxes and wolves) and not in dogs in Europe and North America, where it can cause in red foxes meningoencephalitis and other central nervous system signs.

In their article, Canuti et al. (2024) investigate the presence, distribution and ecology of CanineCV in grey wolf specimens from the Northwest Territories, Canada. CanineCV occurrence appears to be relatively high with 45.3% positive specimens and parvoviral superinfections observed. The authors identify a high CanineCV genetic diversity among the investigated grey wolf specimens, and exacerbated by viral recombination. Phylogenetic analysis reveals the existence of 4 lineages, within each of them strains segregate by geography and not by host origin. This observed geographic segregation is interpreted as being due to the absence of exchange flows between grey wolf host subpopulations. Due to the paucity of knowledge on these circoviruses in wildlife and at the interface between wild and domestic animals, the authors discuss the plausible role of wolves as natural host reservoirs for disease transmission due to long-lasting virus-host coevolution. They are also conscious that additional maintenance hosts could exist in the wild, claiming for further studies to decipher fox circovirus disease ecology and transmission dynamics.

This study underlines the importance of better understanding the transmission ecology and evolution of these Canine circoviruses, and I can only agree. Xiao et al. (2023), a research not referred to in the present work, evidenced CanineCV infection in cats in China, and obtained the first whole genome of cat-derived CanineCV. This emphasizes the importance of monitoring additional animal species and locations in the world to clarify disease ecology and transmission dynamics. A broader sampling of a wide range of animal species in different parts of the world using a species community-based approach is the key to understanding these CanineCV infections.

References:

Marta CANUTI, Abigail V.L. KING, Giovanni FRANZO, H. Dean CLUFF, Lars E. LARSEN, Heather FENTON, Suzanne C. DUFOUR, Andrew S. LANG. 2024. Diverse fox circovirus (*Circovirus canine*) variants circulate at high prevalence in grey wolves (*Canis lupus*) from the Northwest Territories, Canada. bioRxiv, ver. 2 peer-reviewed and recommended by Peer Community in Infections.

<https://doi.org/10.1101/2024.03.08.584028>

World Organization on Animal Health. 2021. Circoviruses. <https://www.woah.org/app/uploads/2021/05/circoviruses-infection-with.pdf> [consulted on July 9th, 2024].

Xiangyu XIAO, Yan CHAO LI, Feng PEI XU, Xiangpi HAO, Shoujun LI, Pei ZHOU. 2023. Canine circovirus among dogs and cats in China: first identification in cats. Front. Microbiol. 14.

<https://doi.org/10.3389/fmicb.2023.1252272>

Reviews

Evaluation round #2

Reviewed by **Arvind Varsani**, 04 July 2024

I am satisfied with the edits.

Evaluation round #1

DOI or URL of the preprint: <https://doi.org/10.1101/2024.03.08.584028>

Version of the preprint: 1

Authors' reply, 16 June 2024

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Decision by [Jean-Francois Guégan](#) , posted 21 May 2024, validated 22 May 2024

The manuscript needs some minor revisions

Dear coauthors,

We have received comments from two reviewers who congratulate you on your work and its quality, and recommend minor revisions. I therefore recommend that you respond to these comments, and resubmit a new version of your manuscript. I've done some reading of your work myself, and bring you my own comments here. Some of them may be erroneous (eg. badgers and their role in CanineCV transmission), but they are given to you to improve the quality and comprehension of your work.

Thank you for submitting your work to PCI Infections.

Jean-Francois Guégan, Recommender

Comments by Recommender

In the title, please add « from the Northwest Territories, Canada »

Abstract : Overall, 72 (45.3%) animals tested positive. Please write « Overall, 72 (45.3%) animals were tested positive (on XXX specimens).

Which statistical test has been used here, and what is the statistical value of this test? (48.3%, $p < 0.001$). Statistical test's values are important and need to be given.

« Sequencing revealed high genetic diversity, further exacerbated by recombination ». Please indicate for which viruses?

« , indicating the co-existence of multiple endemic lineages. » Endemicity is a relative concept depending on spatial scale, here Northwest Territories, Canada. Can you use the expression of endemic lineages here? Does it correspond to sampling bias, or do you have enough knowledge on larger scale to affirm this?

« Finally, viruses from Europe and North America were mixed, indicating that the origin of the four lineages might predate the segregation of European and American wolf and fox populations. » Is there a possibility of post-mixing? Recent switching? Notably through another host species due to the paucity of information as you write on lines 379-380?

Introduction. Lines 86-87. «in foxes from Svalbard and Northern Norway (Urbani et al., 2021) and from Newfoundland and Labrador, Canada (Canuti, Rodrigues, et al., 2022) ». Please indicate that it is the Arctic fox.

Materials and Methods.

Samples. Please add a map of your samplings.

Sequences analyses. I read something about cluster-s in the text see lines 202-203 for instance), so you should explain how you analyze and characterize these clusters here.

Statistical analyses. Line 148. « ...Wald test ». Please write Wald's test.

Results

CanineCV epidemiology among grey wolves

Lines 153-154, and following through all this section. Which test-s has-ve been used, and what are the statistical test' values?

Lines 162-163. (Canuti, Fry, et al., 2022). Better to write Canuti et al. 2022). Please check everywhere.

CanineCV diversity among grey wolves

Lines 199. Badger is a Mustelid and not a Canid, is it? Can you clarify here? So this sentence is not clear to me since your viruses could show a host species range larger than expected and said !

Lines 202-204. « Although a smaller number of samples was available from two of the three investigated areas, a certain clustering based on sampling location could be observed. Three out of four viruses from SSR

were included in clade A, indicating a predominance of viruses from this clade in that location..... » Is it totally subjective when you write a certain clustering, or can this be tested?

Line 209. Please write viruses.

Global epidemiology of fox circoviruses

Lines 252 and following. Please consider my comment on badger.

Discussion. Line 273. OK with Carnivorans for badger. But maybe there's an incomprehension on my part. Redaction should be reviewed in order to avoid such misunderstanding by readers.

CanineCV is endemic among wolves of Northern Canada

Is there a possibility that these viruses may circulate and persist in other tissues and organs? Why do you look at spleen only? The fields of virology and parasitology are full of illustrations where organs or tissues that were not initially accepted as infected habitats, or that were initially rejected as such, subsequently became so.

Does CanineCV facilitate a secondary parvoviral infection?

Line 332 and following. Please give the statistical test, and its statistical value?

Lines 379-380. « ...and that viral diversity in wildlife is largely understudied, so these conclusions could be biased by sample and sequence availability ». I do agree, so you should take into consideration several of my comments (e.g., endemicity, cluster, non-canine host, long-standing separation of European and American fauna and their viruses).

Reviewed by Arvind Varsani, 13 April 2024

The Ms titled "Diverse fox circovirus (*Circovirus canine*) variants circulate at high prevalence in grey wolves (*Canis lupus*)" describes the identification of the CanineCV from 159 grey wolf samples from Canada. The study found a high incidence of positive animals (~45%) and in some cases there were co-infections with other viruses.

Overall, the MS is good and I see nothing wrong with the analyses for the interpretation of the data.

I have a few suggestions to improve the MS

Line 19: Canine circoviruses – plural.

Line 20: I would avoid the use of the term subclade as that only refers to the phylogeny. Rather say strain.

Line 33: change "... and one belonged to a distant clade. In the phylogenetic analysis, the viruses were distributed..." to "... and one belonged to a distant clade. In the phylogenetic analysis, the virus sequences were distributed..."

Line 50: Change to "Circoviruses (family Circoviridae, genus *Circovirus*)"

Line 135: change "built" to inferred. Please edit this throughout the text (e.g. line 301)

Line 320-325: I would be very careful about this. I would not even have this as this is speculative.

Reviewed by anonymous reviewer 1, 25 April 2024

The study from Marta Canuti and colleagues describes the prevalence and diversity of fox circoviruses in grey wolves in Canada and show that these viruses are highly prevalent in grey wolves. They show presence of different viral lineages that form clusters according to geographic origin. The authors show also the presence of recombinant viruses. Moreover, they show that animals infected with circoviruses are more likely to be co-infected with parvoviruses

Overall the study is well conducted and the paper is well written and easy to read.

However the paper can be improved:

- The authors should provide more details on the study population and not only refer to the previous paper on parvoviruses, which was done on more than 300 animals, and in this new study only 159 have been analyzed. Therefore the authors should show more details on the geographic origin, for example a map similar as in the initial paper, and importantly give more details on time period of sample collection for the different samples. Do they see a correlation between variants and sampling period?
- The authors should also explain more in detail why the number of full-length genome sequences was relative low, especially for such a small virus, how did they define the viral load?
- How were samples selected for full-length genome sequencing?

Finally, the authors should add in the title that the study was conducted in Canada.