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Phylogenetic analysis and the spatial spread of arctic rabies virus in Chukotka

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Abstract

Rabies is one of the most common zoonotic diseases of wild mammals in the Arctic. In this article we discuss possible ways of the rabies virus (RABV) incursion into the Chukchi Peninsula after the absence of animal rabies from 1991 to 2008. The aim of the current study is to analyze and document the genetic characteristic and spatial spread of the RABV on the Chukchi Peninsula in comparison with the same in Alaska and other Arctic territories and regions. For over 15 years the genetic diversity of the RABV in the Arctic has been the subject of intensive research. However, until recently, data with regard to the Chukchi Peninsula has been unavailable. An ongoing phylogenetic analysis of 14 full-sized N gene RABV isolates from the Chukchi Autonomous Region of the Russian Federation was carried out. The brain samples were collected from red foxes (9), arctic foxes (1) and dogs (4) in 2017–2024. It was found that all isolates belong to the Arctic genetic lineage. Among them two different pools were identified which demonstrate maximum nucleotide sequence identity with the Arctic-3 isolates from Greenland, the Svalbard Archipelago and Northern Canada. At the same time, different genetic sub-lineages (Arctic-3 v/s Arctic-2 and Arctic-4) were detected in neighboring land areas on both sides of the Bering Sea. A map demonstrating the transcontinental spread of RABV variants between Chukotka and Alaska was prepared based on our own and previously published data.

Keywords

Rabies, Arctic, Chukchi Peninsula, phylogeography, transcontinental spread

Introduction

Rabies has been found to be widespread among wild and domestic animals in the arctic and subarctic regions of Eurasia and North America. The overall history of the study of this zoonotic disease in the Chukchi Peninsula and the adjacent territories of Alaska, Kamchatka and Yakutia, is detailed in several retrospective overviews, from which it can be ascertained that epizootics among sled dogs and wild animals has been known to exist in the region since the 19th century (Karpov 2012; Simon et al. 2012; Huettmann et al. 2017; Botvinkin et al. 2024).

The rabies virus (order Mononegavirales, family Rhabdoviridae, genus *Lyssavirus*, species *Lyssavirus rabies*) was isolated from Arctic animals in the middle of the last century (Plummer 1947; Turevich and Tebyakina 1947). At the end of the last century, the antigenic uniqueness of rabies virus (RABV) isolates from tundra animals was established using the monoclonal antibody P-41 (Schneider et al. 1985). Later, phylogenetic studies made it possible to more accurately characterize the position of RABV isolates from the Arctic among many other geographical variants of this virus. Based on the analysis of the nucleotide sequences of the RABV genome, two large clusters (biotypes) were identified which were found to be either bat-related or dog-related. The overall distribution of bat-related RABVs is apparently confined to the continents of the Americas, while dog-related RABVs are common among dogs and wild carnivores on all continents except Australia and Antarctica (Kuzmin 1999; Bourhy et al. 2008; Davis et al. 2013).

Phylogenetically, the dog-related cluster is divided into six clades: Cosmopolitan, Africa 2, Africa 3, Artic-related, Asian and Indian Subcontinent, whose names reflect their geographical location (Bourhy et al. 2008; Davis et al. 2013; Troupin et al. 2016). The Arctic-related clade is divided into two groups (lineages): Arctic proper, associated with the Arctic regions, and Arctic-like, widespread in Southeast Asia, as well as in the Middle East (Kuzmin et al. 2008). The Arctic lineage, in turn, is divided into four sub-lineages: Arctic-1, Arctic-2, Arctic-3 and Arctic-4 (Kuzmin et al. 2008; Nadin-Davis et al. 2012; Hanke et al. 2016). It is assumed that RABV penetrated into the high latitudes of Eurasia and America from Southeast Asia, and the separation of the Arctic and Arctic-like genetic lineages occurred around 1700 (Kuzmin et al. 2008). In the more distant past, Northeast Asia and Alaska served as a portal for the spread of many animal species and humans. At the junction of the continents, there was a land bridge (the Bering Land Bridge or Beringia), which was covered by the sea about 11,000 YBP, which then led to the relative isolation of faunas (Elias et al. 2016). However, the problem of transcontinental migrations of animals and related pathogens between North America and Eurasia continues to attract attention (Hueffer et al. 2018; Nadin-Davis et al. 2021).

The aim of the current study is to determine the genetic characteristics and spatial spread of the rabies virus by natural host animals on the Chukchi Peninsula in comparison with its spread in Alaska and other Arctic territories.

Materials and methods

The study included 14 RABV isolates from wild and domestic animals (Table 1). The biological materials were collected from 2017 to 2024 in the Chukchi Autonomous Region of the Russian Federation during the ongoing supervision of zoonoses. Distribution of the 14 samples grouped by animal species was as follows: red fox (*Vulpes vulpes* Linnaeus, 1758) – 9, arctic fox (*Vulpes lagopus* Linnaeus, 1758) – 1, and dog (*Canis lupus familiaris* Linnaeus, 1758) – 4. Animal brain samples were first examined in a regional veterinary laboratory using the direct immunofluorescence test (Laboratory techniques in rabies 2018). Positive and suspected samples were sent to the Federal Center for Animal Health in Vladimir, Russian Federation, where after confirming the diagnosis, the nucleotide sequence of the full-size N gene of RABV isolates was determined.

RNA was isolated from a 10% suspension of animal brain tissue using the RiboSorb reagents commercial kit (Central Research Institute of Epidemiology, Moscow, Russian Federation), reverse transcription and amplification of cDNA fragments was carried out using reagents produced by the Syntol Company (Moscow) and primers specific to RABV Arctic and Arctic-like genetic lineages developed at the Reference Laboratory for Rabies and Bovine Spongiform Encephalopathy of the Federal Center for Animal Health (Vladimir, Russian Federation). Using these primers, two overlapping fragments corresponding to the region of the full-size N gene are produced. The first fragment is flanked by D-Oligo primers (5'-ACGGCCAGTACGCTTAACAA-3') and NR878arc (5'-CCCAGTGAACGGAAGTGAAT-3') and the second fragment is flanked by primers F865 (5'-TGAGGAAGAGATAAGAAGAATG-3') and NR1516arc (5'-AGTCTCTTCAGCCATCTCCA-3'). The resulting amplicons were sequenced using primers used in PCR and the BigDye Terminator Cycle Sequencing kit (Applied Biosystems, USA) on an ABI Prism 3100 capillary DNA sequencer (Applied Biosystems, USA). The analysis and alignment of the obtained nucleotide sequences was carried out using the BioEdit version 7.2.5 software package (Hall 1999). The obtained sequences are deposited in GenBank (access numbers are indicated in the names of the isolates in Figures 1 and 2).

The phylogenetic analysis was carried out in the MEGA11 program (Tamura et al. 2021). The model test function was used to identify the best nucleotide substitution model for each dataset. The N gene sequence data was analyzed using Maximum Likelihood (ML) methods. The ML phylogeny was generated using the General time reversible substitution model using gamma distribution with invariant sites (G+I) and employed 100 bootstrap replicates. Bat RABV from North America was selected as the outgroup. The classification of RABV sub-groups from the Arctic, developed by Nadin-Davis et al. (2021), was used for describing phylogenetic groups.

Mapping was performed using the QGIS 3.32.2 program based on OpenStreetMap electronic landscape and geographical maps and open data from GoogleEarth aerospace survey. The points of discovery of the sequenced RABV isolates (10 points for 14 isolates) are plotted on the map of Chukotka in accordance with the geographical coordinates of the locations where infected animals were found. The locations and points of various sub-lineages of Arctic RABV in the adjacent territories of Alaska have been transferred to the map from a previously published work (Kuzmin et al. 2008) using the raster binding tool. The raster layer was bound according to the landmarks of state borders and geographical landscapes by the thin-walled spline method. In a similar way, the known detection points of rabid animals in Chukotka for the period of 1860 to 2023 (Botvinkin et al. 2024) and in Alaska for the period of 1914 to 2013 (Huettmann et al. 2017) were transferred to the map.

Table 1. Rabies virus isolates from Chukotka used in this study

No	Isolate name	GenBank access	Host species	Year	Source of data	Geographical coordinates	
						E	N
1	1335	MN384721	red fox	2017	[5]	179°.11′	66°32′
2	720/68	MN384717	arctic fox	2017	[5]	178°.84′	65°90′
3	720/71	MN 384719	red fox	2017	[5]	173°.21′	64°42′
4	720/69	MN384718	red fox	2017	[5]	171°.70′	65°50′
5	859	MN384720	dog	2018	[5]	161°56′	68°34′
6	770	OQ266763	red fox	2022	this paper	166°45′	68°05′
7	809/1	PP464939	red fox	2023	this paper	171°04′	64°17′
8	857/8	PP464940	red fox	2023	this paper	170°41′	64°68′
9	759	OQ266762	dog	2020	this paper	173°28′	65°50′
10	1074	PP464941	dog	2023	this paper	171°86′	66°95′
11	1406	PP464942	red fox	2023	this paper	171°86′	66°95′
12	547/2	PP464938	dog	2023	this paper	173°21′	64°42′
13	393/3	PP464937	red fox	2024	this paper	170°41′	64°68′
14	393/2	PP464936	red fox	2024	this paper	170°41′	64°68′

Results

The phylogenetic analysis of the almost complete N gene

The phylogenetic tree is constructed using a nearly full-sized nucleoprotein gene (without the last three nucleotides encoding the stop codon, since many GeneBank entries do not have them). Preliminary analysis showed that all studied RABV isolates from Chukotka belong to the genetic sub-lineage Arctic-3. Therefore, for clarity, only the groups of the Arctic-related clade is presented on the tree and only the Arctic-3 sub-lineage is shown in detail, and the rest are given in compressed form to save space in the figure (Fig. 1, Table 2).

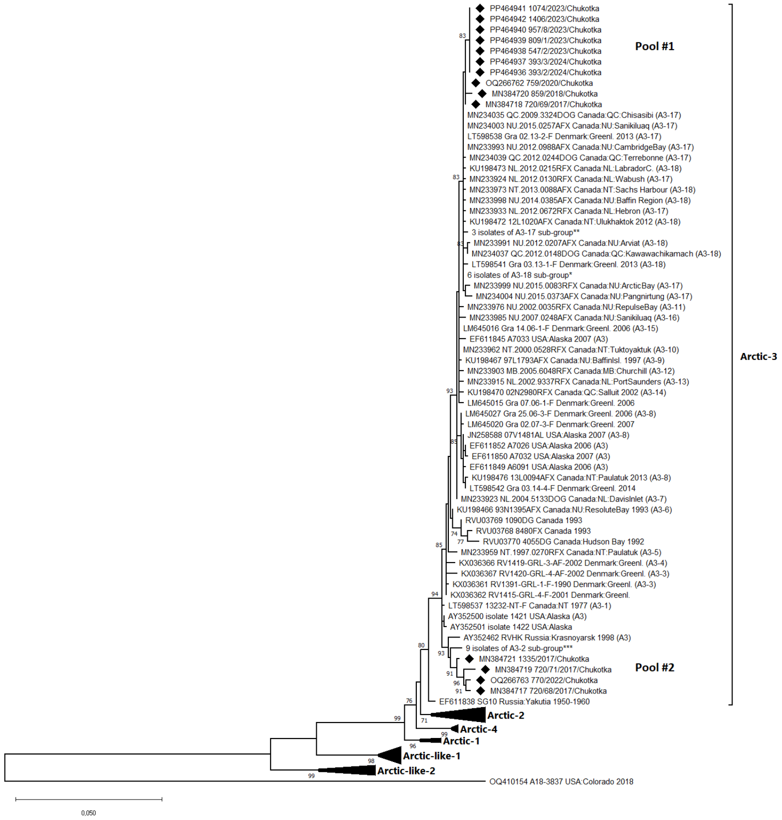

Figure 1. A phylogenetic tree of RABV isolates, built by a nearly full-sized gene N (1350 bp). Boot strap values of less than 70% are hidden. **Legend:** The isolates from Chukotka are marked by diamonds. Isolate record format: GeneBank acc. number/isolate name/year/place of isolation. The subgroups (if known) are indicated in parentheses. Compressed isolates(*,**,***)presented in supplementary materials.

Table 2. Arctic-3 rabies virus isolates compressed on the phylogenetic tree (access numbers and brief information from GenBank)

No	Sub-group	Isolate name	GenBank	Location	Year	Host species
1	A3-18*	0304AFX	MN233994	Canada:NU:Igloolik	2013	arctic fox
2		0663AFX	MN234010	Canada:NU:Sanirajak	2017	arctic fox
3		1842RFX	MN234007	Canada:NU:PondInlet	2016	red fox
4		1432AFX	MN234006	Canada:NU:ResoluteBay	2015	arctic fox
5		3238DOG	MN234033	Canada:QC:Kangirsuk	2009	dog
6		0150AFX	MN233990	Canada:NU:Kugaaruk	2012	arctic fox

No	Sub-group	Isolate name	GenBank	Location	Year	Host species
7	A3-17**	0857RFX	MN233935	Canada:NL:Makkovik	2012	red fox
8		0888RFX	MN233904	Canada:MB:Churchill	2012	red fox
9		0595DOG	MN234015	Canada:ON:Kashechewan	2013	dog
10	A3-2***	0238AFX	MN234054	Canada:QC:Kuujjuarapik	2015	arctic fox
11		13NO643AFX	KU198478	Canada:NU:Grise Fiord	2013	arctic fox
12		1453AFX	MN233969	Canada:NT:Sachs Harbour	2008	arctic fox
13		1385AFX	MN233968	Canada:NT:Ulukhaktok	2008	arctic fox
14		0042AFX	MN233970	Canada:NT:Sachs Harbour	2012	arctic fox
15		0989AFX	MN233972	Canada:NT:Ulukhaktok	2012	arctic fox
16		0305AFX	MN233995	Canada:NU:Igloolik	2013	arctic fox
17		0398DOG	MN233996	Canada:NU:Igloolik	2013	dog
18		0020AFX	MN233885	Canada:Northern Territories	2012	arctic fox

The tree shows that all isolates from Chukotka are divided into 2 pools relative to each other within the Arctic-3 sublineage. Pool #1 is represented by 10 isolates, and pool #2 is represented by 4 isolates. In each of these pools, the level nucleotide sequence identity between isolates is at least 99.6% and 99.3%, respectively, and between representatives of different pools – no more than 98.6%. All isolates that make up pool #1 show the maximum level of affinity with RABV isolates identified in Canada and Greenland from 2009 to 2015. A very high level of relatedness (from 99.48% to 99.93%) is observed within isolates belonging to subgroups A-3-17 and A-3-18 (Nadin-Davis et al. 2021). At the same time, isolates from pool #1 from Chukotka remain on the tree as a separate group due to the fact that the introduction event most likely occurred only once, after which the viruses diverged. Representatives of pool #2 show maximum nucleotide sequence identity with isolates detected in northeastern Canada (98.81-99.56%), in Russia (RVHK isolate, 98.74-99.26%), as well as Alaska, USA (isolate 1421, 98.81-99.33%).

As an additional way to detect related isolates in the BLAST service (https://blast.ncbi.nlm.nih.gov/Blast.cgi) the search for the closest sequences of the N RABV gene was carried out using shorter fragments (400 bp) of this gene for all isolates from Chukotka. As a result, additional closely related sequences of isolates were found for pool # 2, which are not shown in Fig. 1. Using a 571 bp fragment, a new tree was built, which included these isolates (Fig. 2). When comparing short fragments, the maximum nucleotide sequence identity with isolates from pool #2 from Chukotka is shown by 3 isolates identified in the Svalbard Archipelago in 2011 (99.47-99.82%).

Figure 2. A phylogenetic tree of RABV isolates based on a fragment of gene N (571 bp). Bootstrap values of less than 70% are hidden (**Legend** – see Fig.1).

Analysis of the spatial distribution of RABV

As the mapping results show, the registration points of animal rabies are concentrated mainly along the coasts of the northern seas. Individual cases of rabies have been reported on islands and ice fields at a distance of dozens of kilometers from the continental land masses (Fig. 3). The spatial distribution of various genetic RABV sub-lineages in the neighboring territories of Asia and North America have significant differences. In Chukotka, only the sub-lineage Arctic-3 has been found in the latitude range from 65 to 70 degrees north. In Alaska, this sub-lineage is distributed along the coast of the Arctic Ocean about 70 degrees north with two other sub-lineages (Arctic-2 and Arctic-4) found further south along the western coast of the Bering Sea.

Discussion

This study has presented the results of phylogenetic analysis of 14 RABV isolates of the Arctic genetic lineage (sub-lineage Arctic -3) from the Chukchi Peninsula; for 9 of them, the sequences of the N gene have been published for the first time. Epizootics among dogs and Arctic foxes were recorded in Chukotka almost up to the end of the 20th century, but from 1991 to 2008 there was no information about animal rabies. Outbreaks began to be registered again only in 2009, at which time rabies was most often detected in red foxes (Botvinkin et al. 2024).

The most obvious explanation for this is that rabies spread to Chukotka from the neighboring northern territories of Eurasia, which are enzootic for rabies (Karpov 2012). However, in the middle of the last century, sub-lineage Arctic-2 prevailed in Yakutia (Kuzmin et al. 2008); in 2008 and 2016 viruses of this sub-lineage were found in the north of the European part of Russia – Komi Republic, Franz Josef Land Archipelago (Deviatkin et al. 2017). In 1989, RABV of the Arctic-3 sub-lineage was detected near the city of Norilsk, Russian Federation about 3,500 km west of the Chukchi Peninsula (Kuzmin 1999; Kuzmin et al. 2008). Only one of the RABV isolates collected in Yakutia between 1950 and 1960 belonged to sub-lineage Arctic-3, but on the phylogenetic tree it is significantly remote from modern isolates from Chukotka (EF611838, the lowest branch of sub-lineage Arctic-3 in Fig.1). It can only be assumed that the circulation of sub-lineage Arctic-3 continues in the northeast of Siberia.

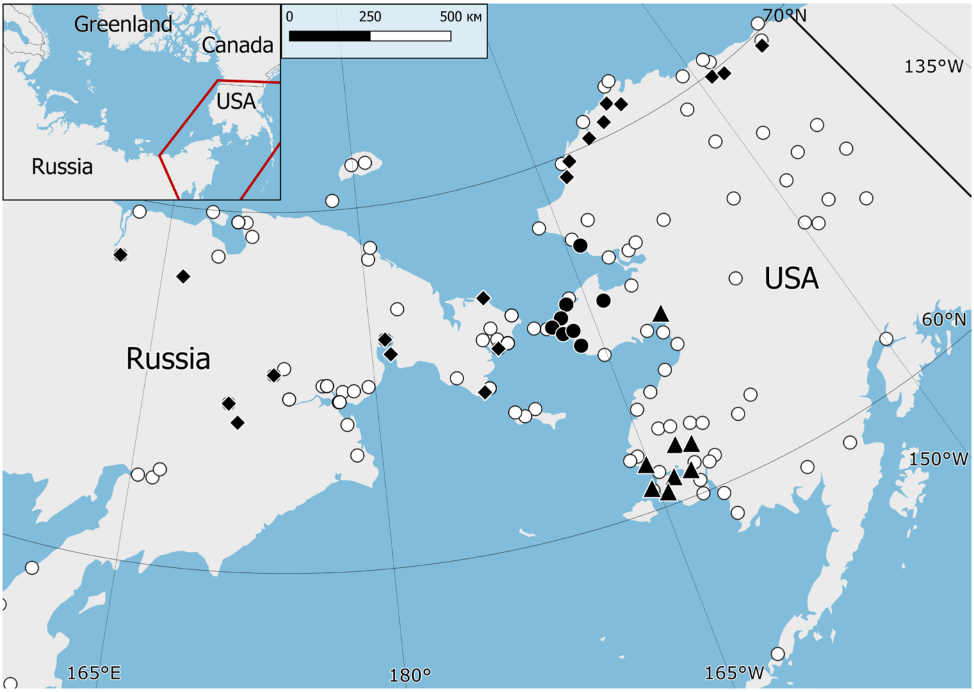

Figure 3. The spatial spread of RABV genetic variants and reported animal rabies cases in Chukotka and Alaska. **Legend:** black circle – Arctic-2, black diamond – Arctic-3, black triangle – Arctic-4, white circle – registration points of animal rabies cases in Chukotka (according to Botvinkin et al. 2024) and Alaska (according to Kuzmin et al. 2008; Huettmann et al. 2017). In the inset, Chukotka and Alaska are highlighted with red lines in the circumpolar area.

The genetic characteristics of RABV isolates from Alaska, Greenland and the northern provinces of Canada have been analyzed in several articles (Kuzmin et al. 2008; Nadin-Davis et al. 2012; 2021; Hanke et al. 2016). According to Nadin-Davis et al. (2021), 18 subgroups (from A3-1 to A3-18) and several clusters of even lower rank within Arctic-3 isolates were additionally identified based on the phylogenetic analysis of complete genomes. According to this classification, the isolates from pool #1 from Chukotka belong to the subgroups Arctic-3-17 or Arctic-3-18. We cannot determine more precisely whether the isolates from Chukotka belong to any of these subgroups, since we used only the sequences of the N gene for the analysis.

Subgroups Arctic-3-17 and 3-18 have dominated all other Arctic rabies lineages in Canada in recent years. According to the authors, the viruses of these two groups originated from a common ancestor that existed around 2007. In 2009 RABVs of these subgroups were first detected in eastern Canada in Quebec and spread westward in subsequent years. It has been established that A-3-17 and A-3-18 are also present in Greenland (Nadin-Davis et al. 2021). On this basis, it can be assumed that the introduction of the ancestors of the Chukchi isolates belonging to pool #1 occurred from the northern territories of Canada, most likely by migrating arctic foxes.

Viruses belonging to pool #2 from Chukotka have been assigned to the Arctic-3-2 subgroup. RABV of this subgroup was first detected in red foxes in Alaska in 1989. Subsequently, Arctic-3-2 RABVs circulated mainly among Arctic foxes on the Arctic islands of Canada, but in recent years have spread to the mainland of the country, where they were the cause of diseases in arctic foxes and dogs on the east coast of Hudson Bay (Nadin-Davis et al. 2021).

In 2011-2012, a massive outbreak caused by RABVs of Arctic-2 and Arctic-3 sub-lineages occurred in the Svalbard Archipelago (Ørpetveit et al. 2022). RABV isolates from pool #2 from Chukotka, discovered 5 years or more after this outbreak, have shown to be very closely related with the isolates of the Arctic-3 sub-lineage from Svalbard.

Generally sub-lineage Arctic-3 circulates along the northern coasts of North America and Eurasia. Many authors have drawn attention to the significant genetic similarity of Arctic-3 isolates from the Arctic regions far remote from each other (Kuzmin et al. 2008; Hanke et al. 2016; Nadin-Davis et al. 2021; Ørpetveit et al. 2022). This was explained by the intensive mixing of the viral population in high latitudes due to the ability of the main natural host of RABV, arctic fox, to long-range migrations across the ice and the coast of the Arctic Ocean (Goldsmith et al. 2016; Fuglei et al. 2019; Baeckland et al. 2021).

At the same time, Arctic-3 isolates from the areas of Alaska closest to Chukotka were assigned to A3-8 sub-group (Nadin-Davis et al. 2021). The sub-groups Arctic-2 and Arctic-4 found on the western coast of Alaska (Kuzmin et al. 2008) have not been found in Chukotka. The Bering Sea is covered with ice during certain periods of the year, but thin ice with patches of open water now prevails, and the ice situation is constantly changing due to climate warming (Stabeno and Bell 2019).

Obviously, at present, the spread of Arctic rabies across the sea ice south of the Bering Strait is difficult or impossible.

The detection of sub-lineage Arctic-3 in Chukotka deserves special attention, as the isolate belonging to this subgroup was previously isolated from a deceased person bitten by a wolf (*Canis lupus* Linnaeus, 1758) in the Siberian Subarctic (Kuzmin 1999; Kuzmin et al. 2008). In Chukotka, rabies in humans was registered in 1982 in the vicinity of Anadyr after a person was bitten by an arctic fox. The virus isolated from the brain of this person reacted positively with MAb P-41 and was assigned to the Arctic group (Selimov et al. 1984). In addition, in 1953-1956, 4 cases of human deaths from rabies were described in Anadyr after dog bites (Botvinkin et al. 2024).

Bat rabies has not been recognized in Chukotka, however we are considering discussing this issue to assess the possibility that there may have been a transcontinental drift. Currently there is no reliable information about bat-related lyssaviruses in northeast Asia. The northernmost observation points of bats (where the species has not been identified) are noted in the forest areas of the Koryak Highlands (about 65 degrees north). However there are no conditions that would allow these animals to live in the tundra of the Chukchi Peninsula. Further south (in Kamchatka and the eastern coast of the Sea of Okhotsk) 4 species of bats have been recorded: *Myotis sibiricus* Kastschenko, 1905; *Myotis petax* Hollister, 1912, *Plecotus ognevi* Kishida, 1927, *Eptesicus nilssonii* Keysler et Blasius,1839 (Vertebrate animals of North-East of Russia,1996; Tiunov et al. 2021).

A similar analysis of data for Alaska was performed earlier (Hueffer et al. 2018). In this work 7 species of bats were mentioned that were mainly found in the southeast of the peninsula, but the presence of the little brown bat (*Myotis lucufugus* LeConte, 1831) was noted on the coast of the Bering Sea north of the Arctic circle (67 degree north). Since 1993, 5 bat rabies cases associated with 3 different bat RABV lineages have been confirmed in Alaska (Hueffer et al. 2018). One of these lineages, shown in Figures 1 and 2 as an out-group, demonstrates the extent of the genetic distance between the bat-related RABVs and the Arctic lineage.There are no bat species common to Alaska and northeast Asia due to the geographical isolation of the bat faunas of these territories (Vertebrate animals of North-East of Russia, 1996). The harsh climatic conditions of the Arctic prevent the natural transcontinental introduction of bat RABVs from Alaska to Chukotka. However, it is impossible to exclude the possibility of long-range importation of bat pathogens by ships, including at high latitudes (Wright and Moran 2011).

Conclusion

We have found that RABV isolates from Chukotka belong to the Arctic-3 genetic lineage and are divided into two pools according to phylogenetic characteristics. Representatives of pool #1 are closest to RABV isolates identified on the north coast of Canada and Greenland, and representatives of the pool #2 are the closest to the viruses detected in the Svalbard Archipelago. After 2009, rabies in Chukotka was detected mainly in red foxes (*V. vulpes*). The results of the study are consistent with previously published data on the extensive circulation of Arctic-3 RABV sub-lineage at high latitudes.

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Author Contributions

Material preparation, data collection, analysis and mapping were mainly performed by Sergei A. Chupin, Ivan D. Zarva, ElenaV. Chernyshova. The first draft of the manuscript was written by Aleksandr D. Botvinkin. All authors read and approved the final manuscript.

Ethics approval. This is an observational study. The Federal Centre for Animal Health Research Ethics Committee (Russia) has confirmed that no ethical approval is required.

Note. Original nucleotide sequence data reported are available in the GenBank databases under the accession numbers OQ266762, OQ266763, MN38417-38420, PP464936-464942.

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