Assessing the extent of community spread caused by mink-derived SARS-CoV-2 variants

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Graphical abstract

Public summary
- SARS-CoV-2 transmission from human to mink is not lineage specific
- Mink-derived SARS-CoV-2 variants keep human-to-human transmission
- At least 12.5% of patients with mink-derived SARS-CoV-2 were caused by human-to-human transmission
Assessing the extent of community spread caused by mink-derived SARS-CoV-2 variants

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**SARS-CoV-2** has recently been found to have spread from humans to minks and then to have transmitted back to humans. However, it is unknown to what extent the human-to-human transmission caused by the variant has reached. Here, we used publicly available SARS-CoV-2 genomic sequences from both humans and minks collected in Denmark and the Netherlands, and combined phylogenetic analysis with Bayesian inference under an epidemiological model, to trace the possibility of person-to-person transmission. The results showed that at least 12.5% of all people being infected with the mink-derived SARS-CoV-2 variants in Denmark and the Netherlands were caused by human-to-human transmission, indicating that this “back-to-human” SARS-CoV-2 variant has already caused human-to-human transmission. Our study also indicated the need for monitoring this mink-derived and other animal source “back-to-human” SARS-CoV-2 in future and that prevention and control measures should be tailored to avoid large-scale community transmission caused by the virus jumping between animals and humans.

**Key words:** SARS-CoV-2; mink; human-to-human transmission

**INTRODUCTION**

**Coronavirus disease 2019 (COVID-19),** which is caused by a novel type of coronavirus (known as SARS-CoV-2, 2019-nCoV, or HCoV-19), has led to more than 100 million infected patients of whom at least 1.2 million have died worldwide as of November 10, 2020, posing a global concern regarding public health. Apart from humans, natural infection of SARS-CoV-2 has been found in several other species of mammals through contact with COVID-19 patients, such as cats, tigers, dogs, and mink. Other animals have also been considered as possibly susceptible hosts (e.g., rabbit, pig, fox, mink, and civet) of SARS-CoV-2 through the entry test with pseudotype virus with S gene of SARS-CoV-2 and affinity abilities between the receptor-binding domain of S and host ACE2 protein. In addition to human-to-animal transmission, SARS-CoV-2 in minks (Neovison vison), initially introduced from humans, could also transmit back to humans. The virus was also shown to obtain some ongoing mink-adapted mutations such as Y453F, F486L, and N501T. Since cross-species transmission has occurred and SARS-CoV-2 can be transmitted back to humans from minks, it is important to clarify whether the “back-to-human” SARS-CoV-2 with ongoing mink-adapted mutations could further lead to transmission among humans. However, the reported study did not reach a conclusion on this point but instead speculated that person-to-person transmission may have occurred. Genomic sequence can be used to trace person-to-person transmission for SARS-CoV-2, which represents an opportunity to confirm whether there was person-to-person transmission for the “back-to-human” SARS-CoV-2, even when epidemiological tracking information was not available or lacking. The main mink fur-producing countries are Denmark, the Netherlands, Poland, and China. Europe is the main production area of mink. Furthermore, mink fur delivered from European farms and sold at auction was worth €1.2 billion in 2016. Since tens of millions of minks have been culled to prevent further mutation and spread of the virus, the mink-derived SARS-CoV-2 variants (defined as those isolated from mink) have caused a catastrophic blow to the mink farming industry.

In this study, we used publicly available SARS-CoV-2 genomic sequences, and combined phylogenetic analysis with Bayesian inference under an epidemiological model, to infer the probability of direct transmission between patients being infected with mink-derived SARS-CoV-2 variants in Denmark and the Netherlands to evaluate the extent of human-to-human transmission caused by mink-derived SARS-CoV-2 variants.

**RESULTS**

**Geographical and phylogenetic distribution of mink-derived SARS-CoV-2 variants**

As of January 6, 2021, there were a total of 761 mink-derived SARS-CoV-2 genomes available. These came from four countries: Canada (4 genomes), Denmark (454 genomes), the Netherlands (291 genomes), and Poland (12 genomes). All these mink-derived SARS-CoV-2 genomes belonged to 15 lineages. For viruses from Canada and Poland, they all belonged to lineage B.1.1 (Figure 1). In the Netherlands, the dominant strains came from lineage B.1.8 (Figure 1). However, the dominant mink-derived variants in Denmark belonged to lineage B.1.1.298 (Figure 1). The widely phylogenetic distribution of mink-derived SARS-CoV-2 genomes suggested that cross-species transmission events of SARS-CoV-2 from human to mink were not lineage specific. Considering the number of mink-derived variants, further analysis was mainly focused on those from lineage B.1.1.298 in Denmark and lineage B.1.8 in the Netherlands.

**Identification of cross-species transmission events**

We used a discrete trait analysis to infer the ancestral host for each branch. An independent cross-species transmission event was considered to occur only if a clade met the following criteria: (1) the direct two branches after the root of the clade have a different host; (2) posterior probability of both branch and ancestral host for the root of the clade is >0.8. In the Denmark dataset, we found three independent cross-species transmission events (Figure 2), all of which were caused by human-to-mink transmission. In addition, we found that six SARS-CoV-2 genomes (in Clade I) from human were closed to mink-derived viral genomes, indicating they were highly likely to be transmitted from mink to human. However, we could not determine how many independent cross-species transmission events occurred due to the low posterior probability of branches. In the Netherlands, three independent cross-species transmission events occurred in lineage B.1.8 (Figure 3). One of these was transmitted from
The Innovation

The probability of direct transmission were three patient pairs (D2/D3, D5/D6, and D1/D3) with bidirectional highly posterior probability of their root and containing humans infected calculation complexity, for further analysis we used only clades with mans infected with mink-derived SARS-CoV-2 variants. To reduce the SARS-CoV-2 variants

Inference of person-to-person transmission events of mink-derived SARS-CoV-2 variants

We then calculated the probability of direct transmission between humans infected with mink-derived SARS-CoV-2 variants. To reduce the calculation complexity, for further analysis we used only clades with highly posterior probability of their root and containing humans infected with mink-derived SARS-CoV-2 variants. In the Denmark dataset, there were three patient pairs (D2/D3, D5/D6, and D1/D3) with bidirectional probability of direct transmission >0.5 (0.998, 0.731, and 0.607, respectively) (Figure 4A). Meanwhile, the number of intermediates between D2/D3, D5/D6, and D1/D3 were estimated as 0.002, 0.271, and 0.412, respectively (Figure 4B). All of these results suggested that these three patient pairs were more likely to be transmitted from each other directly. In the Dutch dataset, we also found two pairs of patients in Clade I (N7/N8 and N3/N4) with bidirectional probability of direct transmission >0.5 (0.95 and 0.931, respectively) (Figure 4C). In addition, the number of intermediates between N7/N8 and N3/N4 were estimated as 0.05 and 0.069, respectively (Figure 4D). There were also two pairs of patients in Clade II (N10/N11 and N13/N14) with bidirectional probability of direct transmission >0.5 (0.989 and 0.978, respectively) (Figure 4E). In addition, the number of intermediates between N10/N11 and N13/N14 were estimated as 0.011 and 0.022, respectively (Figure 4F).

Validation of the direct transmission events

Since limited variations detected in mink-derived SARS-CoV-2 variants could not result in a highly resolved phylogeny, we next wanted to test how phylogenetic uncertainty might affect the result by repeating the analysis based on ten trees randomly selected from the MCMC chain. In the Danish dataset, the cluster with D1, D2, and D3 always contained a patient pair with highly bidirectional probability of direct transmission (Figure 5). However, the bidirectional probability of direct transmission for D5 and D6 was lower than 0.5 in two randomly selected trees, indicating that the inference of direct transmission between D5 and D6 could be affected by the phylogenetic uncertainty (Figure 5). In this case, we concluded that only one person-to-person transmission event occurred in the Danish dataset. For the Dutch dataset, we found a pattern similar to that of the Danish dataset whereby the phylogenetic uncertainty highly affected the inference of who infected whom. However, there was at least one direct transmission event with high bidirectional probability that occurred in each cluster for ten randomly selected phylogenies (Figure 6). Besides, we found that N10–N14 are all employees in the same mink farm, indicating that the direct transmission between them could be more likely to occur. In this case, we concluded that at least two person-to-person transmission events occurred in the Dutch dataset. In summary, we identified at least three direct transmission events with high bidirectional probability among humans infected with mink-derived SARS-CoV-2 variants in Denmark and the Netherlands. This accounted for 12.5% of all people infected with mink-derived SARS-CoV-2 variants in this study.

We also found some mutations arising in the "back-to-human" SARS-CoV-2 genomes compared with their closely related mink-derived genomes. In the Danish dataset, C2062T (located at the S terminal of SARS-CoV-2 genome) was detected in D4. However, this mutation was not detected in other closely related human SARS-CoV-2 and closest mink-derived variant. A nonsynonymous mutation (C12008T resulting in Leu3915Phe in ORF1ab) were lost in both D5 and D6 compared with their closest related mink-derived variant. In the Dutch dataset, more mutations were detected. Among them, we found that there was no common mutation shared by all human genomes. Together with the limited number of mink-derived SARS-CoV-2 genomes from humans, this means we are currently unable to determine whether there are human adaptive mutations.

DISCUSSION

Since the SARS-CoV-2 carried by mink could be transmitted back to humans,15 this led to the mass culling of infected animals, posing a huge threat to public health and the economy. The first thing we need to evaluate is whether the variant can continue to spread from person to person and to study the extent of the current human-to-human transmission. We found that the phylogenetic types of dominant strains in different countries were not consistent (Figure 1), indicating that the cross-species transmission events of SARS-CoV-2 from human to mink were not lineage specific. In other words, many phylogenetic
subtypes of SARS-CoV-2 can be transmitted from human to mink. However, whether all subtypes of the SARS-CoV-2 can be transmitted to mink is still unknown and needs further research and confirmation. Several independent cross-species transmission events were identified in this study, which contained both human-to-mink and mink-to-human directions. We also detected at least three human-to-human transmission events with highly bidirectional probability. However, we are not sure who infected whom, mainly due to the phylogenetic uncertainty caused by limited mutations. The phylogenetic uncertainty also caused a different number of direct transmission events for each dataset.

Figure 2. Identification of cross-species transmission events in Danish dataset. Maximum clade credibility phylogeny for the Danish dataset. Branch colors indicate the most probable ancestral host. For selected nodes, colored numbers show the posterior probabilities of ancestral host, and numbers in black are clade posterior probabilities.
(Figures 5 and 6), yet there was always one direct transmission event with high bidirectional probability that occurred in each dataset. Under these circumstances, we were able to conclude that there were at least three direct transmission events identified in Denmark and the Netherlands, accounting for at least 12.5% of all people infected with mink-derived SARS-CoV-2 variants in this study. However, the extent of human-to-human transmission caused by mink-derived SARS-CoV-2 variants was considered to be underestimated. The reasons for this are summarized as follows. First, not all viral genomes of patients infected with mink-derived SARS-CoV-2 variants were immediately available. Second, the criteria for identifying direct transmission events were strict in this study, leading to a low true-positive ratio. In this regard, the mink-derived SARS-CoV-2 variants in human and the subsequent extent of person-to-person transmission caused by this variant should be continuously monitored. Despite mink being the only species so far that could be easily infected by humans with SARS-CoV-2 and then transfer the mutants back to humans again, this phenomenon might also exist in other non-human mammals that could be infected by SARS-CoV-2 and are in frequent contact with humans. Under these circumstances, the contact between humans and susceptible animals should be cautious to prevent humans from transmitting SARS-CoV-2 to animals and thus prevent the virus from continuously circulating and evolving in the animals. This will not only minimize the impact of the SARS-CoV-2 on the breeding industry, as increased mortality was detected in farmed minks that were positive to SARS-CoV-2 RNA, but also decrease the probability of generating further novel and unpredictable mutants of SARS-CoV-2 within animals, thereby threatening public health.

Figure 3. Identification of cross-species transmission events in the Dutch dataset. Maximum clade credibility phylogeny for the Dutch dataset. Branch colors indicate the most probable ancestral host. For selected nodes, colored numbers show the posterior probabilities of ancestral host, and numbers in black are clade posterior probabilities.
MATERIALS AND METHODS

Data collection, filtration, and pre-processing

We retrieved genomic data from GISAID on January 6, 2021. We discarded genomic data with no exact collection date (accurate to days). Mink-derived sequences were defined as SARS-CoV-2 genomes isolated from minks. Since the most dominated mink-derived SARS-CoV-2 genomes belonged to B.1.1.298 and B.1.8 for Denmark and the Netherlands, only human-derived and mink-derived SARS-CoV-2 genomes from these two lineages for Denmark and the Netherlands were used. Genomic sequences were aligned using Mafft v7.310. We then trimmed the uncertain regions in 3’0 and 5’0 terminals and also masked 30 sites (Table S1) that are highly homoplastic and have no phylogenetic signal as previously noted (https://virological.org/t/issues-with-sars-cov-2-sequencing-data/473).

Phylogenetic analysis

As recombination could impact the evolutionary signal, we searched for recombination events in these SARS-CoV-2 genomes using RDP4. No evidence for recombination was found in our dataset. We used jModelTest v2.1.6 to find the best substitution model for each dataset from different countries according to the Bayesian information criterion. The best substitution model for datasets from Denmark and the Netherlands was HKY and GTR + I, respectively. The list of genomic sequences used in this study are provided in Table S2. The list of genomic sequences used in this study was openly shared via the GISAID initiative.

We then used the Bayesian Markov chain Monte Carlo (MCMC) approach implemented in BEAST v1.10.4 to derive a dated phylogeny for SARS-CoV-2. We conducted three replicate runs for each 100 million MCMC steps with sampling parameters and trees every 10,000 steps. As genomic sequences used in each dataset were all from the same lineage, we assumed that they followed a strict molecular clock. The estimation of the most appropriate coalescent models for Bayesian phylogenetic analysis was determined using both path-sampling and stepping-stone models. The best-fitting combination of prior of coalescent model was Bayesian skyline tree prior for both datasets (Table S3). Tracer 1.7.1 was then used to check the convergence of MCMC chain (effective sample size >200) and to compute marginal posterior distributions of parameters, after discarding 10% of the MCMC chain as burn-in. We also reconstructed the host for each ancestral branch by using the Bayesian asymmetric discrete trait evolution model under the Bayesian stochastic search variable selection framework. We determined whether there was sufficient temporal signal in each dataset, as it was the prerequisite for obtaining a reliable inference when performing phylodynamic analysis. Bayesian evaluation of temporal signal (BETS) was used to evaluate the temporal signal in each dataset. BETS relies on the comparison of marginal likelihoods of two models: the heterochronous (with tip date) and isochronous (without
Analyses were performed with at least three independent replicates of 100 million MCMC steps each, with sampling parameters and trees every 10,000 steps, with the best substitution model and most appropriate combination of molecular clock and coalescent models determined above for each dataset. The marginal likelihoods were estimated by path sampling. The Bayes factor (BF) was then calculated based on the likelihoods of two models (heterochronous and isochronous). If the log BF was >5 (heterochronous model against isochronous model), there was sufficient temporal signal in this dataset. The log BF was estimated as 227 and 458 for datasets from Denmark and the Netherlands, respectively, suggesting that the temporal signal was sufficiently strong. For convenience, we renumbered all mink-derived SARS-CoV-2 variants from humans (Table S4).

Transmission analysis
As viral genomes were incompletely sampled and the pandemic is currently ongoing, TransPhylo v1.4.4 was used to infer the transmission tree using the dated phylogeny generated above as input. The generation time (i.e., the time gap from infection to onward transmission, denoted $G$) of COVID-19 was previously estimated as 4.8 ± 1.7 days, and we used these values to compute the shape and scale parameter of a gamma distribution of $G$ using the R package epitrix. The distribution of sampling time (i.e., the time gap from infection to detection and sampling) was set equal to the distribution of generation time. We performed the TransPhylo analysis with at least 500,000 iterations simultaneously estimating the transmission tree, the proportion of sampling, the within-host coalescent time $N_e$, and the two parameters of the negative binomial offspring distribution (which represents the number of secondary cases caused by each infection). All results were generated after discarding the first part of the MCMC chains as burn-in (Table S5). The MCMC mixing and convergence was assessed on the basis of the effective sample size of each parameter (>200) and by visual examination of the MCMC traces. The probabilities of direct transmission from one host to another were estimated as the proportion of MCMC samples in which this direct transmission event occurred. The expected numbers of intermediates from one host to another were estimated as the average across the MCMC samples of the number of intermediates between the two hosts.

Evaluation of phylogenetic uncertainty on the inference of transmission chain
Since the inference of transmission tree and further estimation of the probability of directed transmission were solely based on a dated phylogeny, we then tested whether the uncertainty in phylogeny affected the result. Ten dated phylogenetic trees were randomly selected from the MCMC chains for TransPhylo analysis. The parameter setting was the same as described above. The estimated bidirectional probability of direct transmission for each patient pair was visualized by Cytoscape v3.8.2.
Figure 6. Influence of phylogenetic uncertainty on the inference of direct transmission pair for the Dutch dataset. Network graph of direction transmission pair for the Dutch dataset estimated from ten randomly selected trees from MCMC chains. Nodes represent patients, and the line between each node represents the direct transmission. The yellow and green nodes represent nodes from Clusters I and II, respectively. The width of the line is proportional to the bidirectional probability of direct transmission between each patient. If the bidirectional probability of direct transmission between each patient was >0.5, the line is purple, otherwise it is black.
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AUTHOR CONTRIBUTIONS

L.W., Y.B., and G.F.G. designed and coordinated the study. L.W. collected data and performed the analysis. L.W., X.D., Y.B., and G.F.G. contributed to the critical interpretation of the results. L.W. wrote the paper. L.W., X.D., Y.B., and G.F.G. revised the manuscript. All authors reviewed and edited the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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