Risk assessment of SARS-CoV-2 variants that have been selected in mink.

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Summary:

SARS-CoV-2, the virus that causes COVID-19 in humans, can infect domesticated animals.

There have been several outbreaks of SARS-CoV-2 in mink farms across Europe in the Netherlands, Spain and Denmark and also in USA.

As the virus passes through the farm between mink that are densely housed, mutations that enhance replication in mink can be selected.

Some humans have become infected as a result of contact with the infected mink, and viruses carrying mutations that were selected for in mink have now passed into humans in Denmark.

The mutations of concern are in the spike protein of mink-adapted SARS-CoV-2 isolates. Spike is the protein on the surface of the virus particle by which the virus attaches to its target cells. Spike docks the virus onto target cells by binding to a cell surface protein ACE2. Spike is also recognised by the immune system and is a major target for antibodies that neutralize virus.

The sequence where spike binds is different in human and mink ACE2, and so it is not surprising that viruses evolve in mink to optimize their ability to bind the mink ACE2.

Antibodies that neutralize SARSCoV-2 infectivity often target the interface between ACE2 and spike. Mutations in spike that affect ACE2 interaction might also affect the efficacy of antibodies to inhibit the virus. Some data has been presented by the Danish group that a virus carrying 4 mutations associated with mink adaptation is less well neutralized by human convalescent sera.

This paper addresses the key questions:

- What effect do mink adaptations have on the ability to viruses to infect, cause disease and transmit between humans?
- Are there any circumstances in which these mutants might pose an additional risk?

We conclude that

- Mink adapted viruses can infect humans (high confidence).
- There is no evidence to date that the disease caused by mink adapted viruses in humans is more severe (moderate confidence).
- Single mutations that confer mink adaptation do not increase transmission of virus in humans, but viruses with combinations of mutations that have arisen during replication in mink have sustained community transmission in Denmark (moderate confidence).
- Some mink adaptations in Spike result in decreased antibody neutralization (low confidence).
- The loss of neutralization is more evident in sera with low amounts of antibody. This concern should be considered in the context that the effects of the mink adaptations are not greater

than those seen for other variants of SARS-CoV-2 viruses recently reported to carry spike mutations that have naturally arisen during circulation in humans (low confidence).

- For all the spike variants where decreased neutralization is observed, there is a possibility that the mutations might restore the ability of the virus to replicate and spread in people who have antibodies following a first infection or vaccination. This could eventually lead to a requirement for vaccine update, as seen for influenza viruses (low confidence).

Recommendations

1. The following experiments are recommended:
    a. Compare the entry of viruses with the different spike mutations into cells that have the mink or the human ACE2 receptor
    b. Measure how well the mink-adapted virus replicates in (primary) human airway cells in comparison to the current circulating SARS-CoV-2 human strains.
    c. Assess neutralization of live virus variants or pseudoviruses bearing spike variants by convalescent sera, monoclonal antibodies and sera from vaccines recipients.
    d. Test for protection from infection or disease in animals that are pre-infected or immunized with wild type Spike virus or vaccines followed by challenge with viruses bearing Spike variants.
2. Surveillance programmes should be alert to the emergence of spike variants and a pipeline established to risk assess them for changes in antigenicity and fitness in human airway cells.
3. Formal surveillance should also be considered for other animal sources of zoonotic transmission including domesticated and companion animals.

Epidemiology of SARS-CoV-2 in mink

Based on current evidence, the risk of introduction of SARS-CoV-2 from people to animals is high in many species of mammals including mustelids, such as mink and ferrets, as well as racoon dogs; but low er in others such as rabbits; and other farmed livestock specieshttps://onlinelibrary.wiley.com/doi/10.1111/mam.12225. Amongst companion animals occasional transmissions from infected humans to contact cats and dogs has been reported but such infections are self limiting (OIE 2020) https://www.oie.int/scientific-expertise/specific-information-and-recommendations/questions-and-answers-on-2019novel-coronavirus/

Denmark hosts a mink farming industry with more than 17 million mink. SARS-CoV-2 has infected the mink and outbreaks have spread to more than 200 farms by November 2020 despite application of intensive measures to control.

Sequence analyses place the Danish mink viruses into seven clusters. A small cluster of mink-associated human cases with 5 mutations in the spike protein is referred to as cluster 5. Cluster 5 virus has only been detected on five Danish mink farms. Of 12 human 'cluster 5' associated cases in Denmark, at least 11 live in the region close to where the mink are farmed. Amongst these 12 human cases, four have been reported to be directly linked to some form of contact with three mink farms.

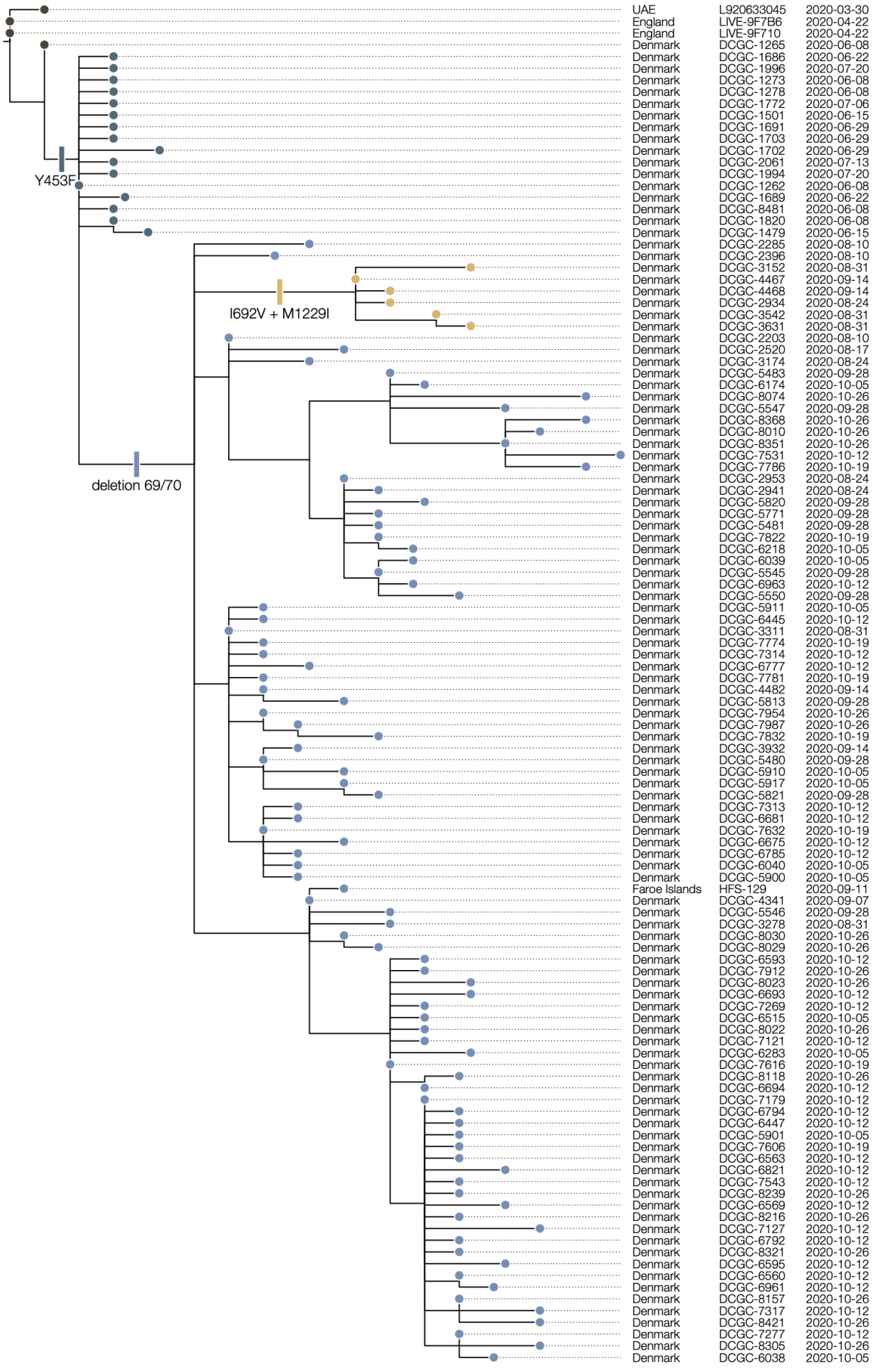
Other countries with mink farming industries include Netherlands, Spain and USA. All have reported outbreaks of SARS-CoV-2. A detailed analysis of Netherlands outbreaks has confirmed the virus has passed to mink from humans and from mink back to humans again carrying hallmark mink adapting mutations (1). Outbreaks were first detected on Dutch mink farms in late April and by June 26th 16 farms were found positive for SARS-Cov-2 virus. In Utah, Wisconsin and Michigan USA there have been large outbreaks on mink farms in which thousands of mink have died https://www.avma.org/javma-news/2020-11-15/sars-cov-2-kills-thousands-minks-utah.

However there has not until now been any reports of widespread community transmission of the mink adapted viruses in humans.

Analysis of the sequence of SARS-CoV2- viruses associated with mink.

The 5 spike mutations that designate cluster 5 of the Danish outbreaks are Y453F, I692V, M1229I and the deletion of two amino acids at sites 69 and 70 (69-70deltaHV). Only 12 human cases have all 5 mutations but the wider lineage of Danish human cases show mutations occurring with the Y453F amino acid change (cases from June and July), deletion at 69/70 (first cases in August), and finally I692V and M1229I (September). No further human cases of cluster 5 have been seen in Denmark since September despite ongoing genomic surveillance there. Y453F has been associated with mink infections in the Netherlands and in some variants transmitted to humans [1]. Virus genomes carrying mutations Y453F and (69-70deltaHV) have continued to be detected in human cases in Denmark during October (Figure 1).

The variant comprising Y453F + 69-70deltaHV appears to have established sustained transmission in Denmark but there is no evidence yet that it has spread to other countries. The degree to which transmission of this variant in Denmark occurs via human-to-human transmission, as opposed to multiple independent transmissions from the infected mink population, is not yet clear.



UAE	L920633045	2020-03-30
England	LIVE-9F7B6	2020-04-22
England	LIVE-9F710	2020-04-22
Denmark	DCGC-1265	2020-06-08
Denmark	DCGC-1686	2020-06-22
Denmark	DCGC-1996	2020-07-20
Denmark	DCGC-1273	2020-06-08
Denmark	DCGC-1278	2020-06-08
Denmark	DCGC-1772	2020-07-06
Denmark	DCGC-1501	2020-06-15
Denmark	DCGC-1691	2020-06-29
Denmark	DCGC-1703	2020-06-29
Denmark	DCGC-1702	2020-06-29
Denmark	DCGC-2061	2020-07-13
Denmark	DCGC-1994	2020-07-20
Denmark	DCGC-1262	2020-06-08
Denmark	DCGC-1689	2020-06-22
Denmark	DCGC-8481	2020-06-08
Denmark	DCGC-1820	2020-06-08
Denmark	DCGC-1479	2020-06-15
Denmark	DCGC-2285	2020-08-10
Denmark	DCGC-2396	2020-08-10
Denmark	DCGC-3152	2020-08-31
Denmark	DCGC-4467	2020-09-14
Denmark	DCGC-4468	2020-09-14
Denmark	DCGC-2934	2020-08-24
Denmark	DCGC-3542	2020-08-31
Denmark	DCGC-3631	2020-08-31
Denmark	DCGC-2203	2020-08-10
Denmark	DCGC-2520	2020-08-17
Denmark	DCGC-3174	2020-08-24
Denmark	DCGC-5483	2020-09-28
Denmark	DCGC-6174	2020-10-05
Denmark	DCGC-8074	2020-10-26
Denmark	DCGC-5547	2020-09-28
Denmark	DCGC-8368	2020-10-26
Denmark	DCGC-8010	2020-10-26
Denmark	DCGC-8351	2020-10-26
Denmark	DCGC-7531	2020-10-12
Denmark	DCGC-7786	2020-10-19
Denmark	DCGC-2953	2020-08-24
Denmark	DCGC-2941	2020-08-24
Denmark	DCGC-5820	2020-09-28
Denmark	DCGC-5771	2020-09-28
Denmark	DCGC-5481	2020-09-28
Denmark	DCGC-7822	2020-10-19
Denmark	DCGC-6218	2020-10-05
Denmark	DCGC-6039	2020-10-05
Denmark	DCGC-5545	2020-09-28
Denmark	DCGC-6963	2020-10-12
Denmark	DCGC-5550	2020-09-28
Denmark	DCGC-5911	2020-10-05
Denmark	DCGC-6445	2020-10-12
Denmark	DCGC-3311	2020-08-31
Denmark	DCGC-7774	2020-10-19
Denmark	DCGC-7314	2020-10-12
Denmark	DCGC-6777	2020-10-12
Denmark	DCGC-7781	2020-10-19
Denmark	DCGC-4482	2020-09-14
Denmark	DCGC-5813	2020-09-28
Denmark	DCGC-7954	2020-10-26
Denmark	DCGC-7987	2020-10-26
Denmark	DCGC-7832	2020-10-19
Denmark	DCGC-3932	2020-09-14
Denmark	DCGC-5480	2020-09-28
Denmark	DCGC-5910	2020-10-05
Denmark	DCGC-5917	2020-10-05
Denmark	DCGC-5821	2020-09-28
Denmark	DCGC-7313	2020-10-12
Denmark	DCGC-6681	2020-10-12
Denmark	DCGC-7632	2020-10-19
Denmark	DCGC-6675	2020-10-12
Denmark	DCGC-6785	2020-10-12
Denmark	DCGC-6040	2020-10-05
Denmark	DCGC-5900	2020-10-05
Faroe Islands	HFS-129	2020-09-11
Denmark	DCGC-4341	2020-09-07
Denmark	DCGC-5546	2020-09-28
Denmark	DCGC-3278	2020-08-31
Denmark	DCGC-8030	2020-10-26
Denmark	DCGC-8029	2020-10-26
Denmark	DCGC-6593	2020-10-12
Denmark	DCGC-7912	2020-10-26
Denmark	DCGC-8023	2020-10-26
Denmark	DCGC-6693	2020-10-12
Denmark	DCGC-7269	2020-10-12
Denmark	DCGC-6515	2020-10-05
Denmark	DCGC-8022	2020-10-26
Denmark	DCGC-7121	2020-10-12
Denmark	DCGC-6283	2020-10-05
Denmark	DCGC-7616	2020-10-19
Denmark	DCGC-8118	2020-10-26
Denmark	DCGC-6694	2020-10-12
Denmark	DCGC-7179	2020-10-12
Denmark	DCGC-6794	2020-10-12
Denmark	DCGC-6447	2020-10-12
Denmark	DCGC-5901	2020-10-05
Denmark	DCGC-7606	2020-10-19
Denmark	DCGC-6563	2020-10-12
Denmark	DCGC-6821	2020-10-12
Denmark	DCGC-7543	2020-10-12
Denmark	DCGC-8239	2020-10-26
Denmark	DCGC-6569	2020-10-12
Denmark	DCGC-8216	2020-10-26
Denmark	DCGC-7127	2020-10-12
Denmark	DCGC-6792	2020-10-12
Denmark	DCGC-8321	2020-10-26
Denmark	DCGC-6595	2020-10-12
Denmark	DCGC-6560	2020-10-12
Denmark	DCGC-6961	2020-10-12
Denmark	DCGC-8157	2020-10-26
Denmark	DCGC-7317	2020-10-12
Denmark	DCGC-8421	2020-10-26
Denmark	DCGC-7277	2020-10-12
Denmark	DCGC-8305	2020-10-26
Denmark	DCGC-6038	2020-10-05

Figure 1 | A phylogenetic tree of Danish SARS-CoV-2 genomes isolated from humans and related to mink-associated cluster 5 (yellow) with the sequence of spike mutations labelled. Only non-identical genomes are shown. The vertical bars denote the branch on which the labelled mutations are inferred to have occurred. All descendent viruses to the right of these then have those mutations.

Y453F has been seen only occasionally in the spike glycoprotein in virus genomes isolated from human cases in different parts of the world (see Table 1). It is unknown to what extent these cases have been exposed to infected mink, or have travelled to areas where mink-associated infections have been reported. The repeated appearance of the Y453F mutation in genomes from mink or mink-associated cases suggests this mutation is selected for in farmed mink populations, perhaps because it enhances binding to the mink ACE2 receptor. The alternative explanation, that the Y453F mutation is selectively neutral and arose by chance, is less likely but cannot at present be formally ruled out.

Onwards human-to-human spread in Denmark of viruses carrying Y453F indicates that this mutation doesn't adversely affect the ability of the virus to infect and transmit in humans. The persistent lineage also carries the 69-70deltaHV deletion.

Table 1 | Human SARS-CoV-2 genomes with the Y453F mutation.

Virus name	GISAID ID	Lineage	Location	Date
Russia/SPE-RII-30769S	EPI_ISL_596228	B.1.1	Russia / Saint Petersburg	20-AUG-2020
USA/UT-UPHL-201030072	EPI_ISL_594062	B.1.5	USA / Utah	1-OCT-2020
Australia/VIC9155	EPI_ISL_565416	B.1.1	Australia / Victoria	21-AUG-2020
Switzerland/AG-ETHZ-280083	EPI_ISL_560418	B.1.1	Switzerland / Aargau	7-SEP-2020
Netherlands/NB-EMC-271	EPI_ISL_523393	B	Netherlands / Noord Brabant	2020
Netherlands/NB-EMC-270	EPI_ISL_523392	B	Netherlands / Noord Brabant	2020
Netherlands/NB-EMC-267	EPI_ISL_523390	B	Netherlands / Noord Brabant	2020
Netherlands/NB-EMC-265	EPI_ISL_523388	B	Netherlands / Noord Brabant	2020
Switzerland/BE-ETHZ-190026	EPI_ISL_500890	B.1.1	Switzerland / Bern	7-JUL-2020
Switzerland/ZG-ETHZ-190022	EPI_ISL_500887	B.1.1	Switzerland / Zug	7-JUL-2020
South Africa/KRISP-0303	EPI_ISL_487348	B.1	South Africa / KZN	25-JUN-2020

The deletion of two residues at position 69/70 in spike is seen in 1814 SARS-CoV-2 genomes from numerous countries. In ~85% of these genomes the deletion co-occurs with the N439K Spike mutation (an amino acid change in the receptor binding motif that increases binding affinity to ACE2 [2]). However the N439K mutation is frequently observed in the absence of the 69-70deltaHV deletion (Figure 2). Specifically, Thomson et al. [2] describe two independent lineages with N439K in humans and the association of 69-70deltaHV with N439K is seen in the larger lineage, which circulates mostly in Europe. The 69-70deltaHV deletion is also seen sporadically in the absence of N439K (a total of 75 genomes, excluding the Danish ones associated with the mink outbreak). Figure 2 shows the number of times each of these mutations occur in the same genome across currently available human SARS-CoV-2 sequences.

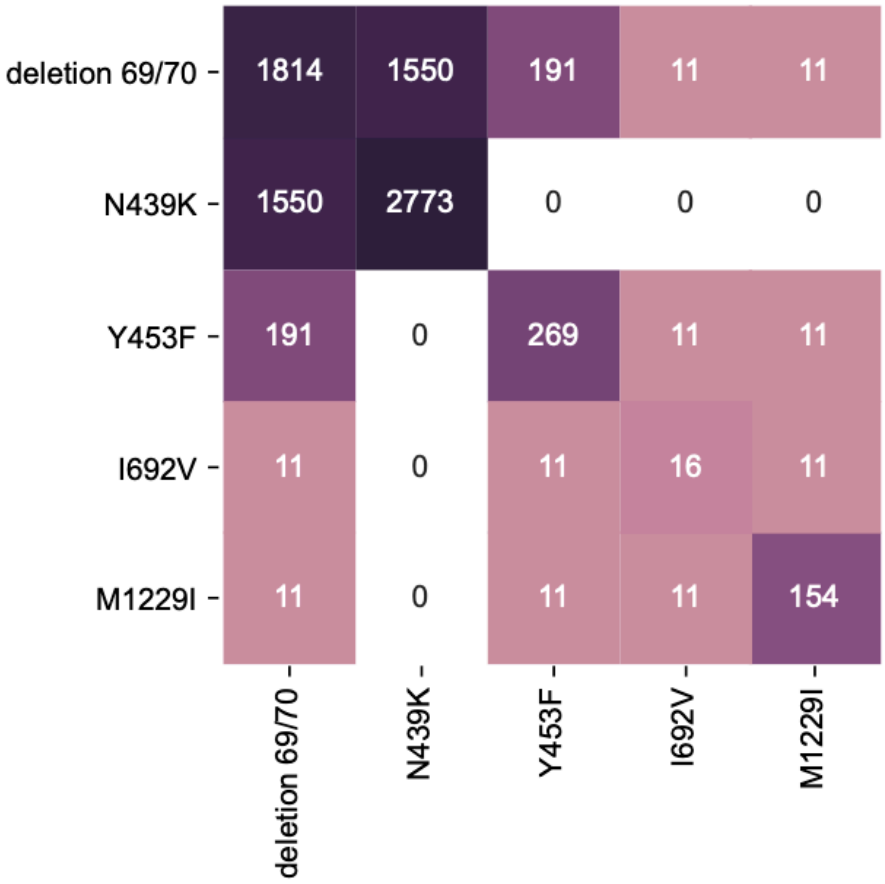


Figure 2 | The co-occurrence of spike mutations across 179,933 human SARS-CoV-2 genomes (collated on 8-Nov-2020).

The mutation M1229I has been seen in 154 human cases without known mink exposure with multiple independent occurrences but not in association with the other mutations discussed here.

Finally the mutation I692V has not been seen outside the 'cluster 5' cases in Denmark.

Conclusions from genomic data

The ‘cluster 5’ variant with 4 Spike mutations does not seem to have become established in humans, though continued genomic surveillance of SARS-CoV-2 in mink and mink-associated human cases is clearly warranted.

Y453F is strongly associated with mink, can cause human infections and is being transmitted among humans. In the Danish lineage this variant seemed to have become established in the local community once it also acquired the 69-70deltaHV deletion. The degree to which epistatic interactions between these mutations exist and are compensatory, or whether their co-occurrence was a chance event, requires further investigation.

However the 69-70deltaHV deletion is very strongly associated with another receptor binding domain mutation N439K which has established significant transmission lineages in the UK and other countries which suggests a possible interaction between them.

References pertinent to the sequence analysis

1. Oude Munnink BB, Sikkema RS, Nieuwenhuijse DF, Molenaar RJ, Munger E, Molenkamp R, et al. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. Science. 2020 [cited 11 Nov 2020]. doi:10.1126/science.abe5901

2. Thomson EC, Rosen LE, Shepherd JG, Spreafico R, da Silva Filipe A, Wojcechowskyj JA, et al. The circulating SARS-CoV-2 spike variant N439K maintains fitness while evading antibody-mediated immunity. Cold Spring Harbor Laboratory. 2020. p. 2020.11.04.355842. doi:10.1101/2020.11.04.355842

Structural analyses support that the mink adaptation 453F impacts Spike:ACE2 interaction

Figure 3 below illustrates the interaction between spike protein and human ACE2. This structure was solved at The Crick Institute and is published by Benton et al. Nature 2020.

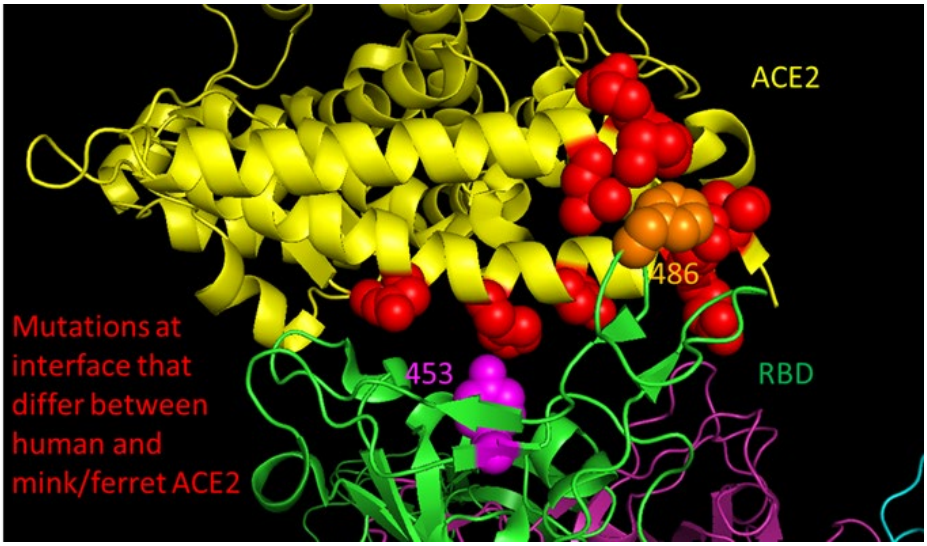


Figure 3: interaction between SARS-CoV-2 Spike protein and ACE2 receptor.

Amino acids from the ACE2 protein at the interacting surface with Spike that are different between human and mink are shown in red. The location of the mink-adapting spike mutationY453F is coloured in magenta. It sits opposite amino acid 34 in ACE2 that differs between human (H histidine) and mink (Y tyrosine). A second mutation F486L reported in some mink viruses in an April outbreak in Netherlands is coloured orange.

This picture shows several differences between the ACE2 receptor of mink and humans that might drive the virus to select for adaptive mutations in mink.

The sequence of ACE2 varies by only 2 amino acids from mink to ferret and the region that interacts with spike is not different. Spike from human SARS-CoV-2 isolates interacts poorly with ferret ACE2, so, in ferrets, there is considerable pressure on the virus to select for mutations that repair the poor interaction. https://www.biorxiv.org/content/10.1101/2020.06.17.156471v1.full.pdf

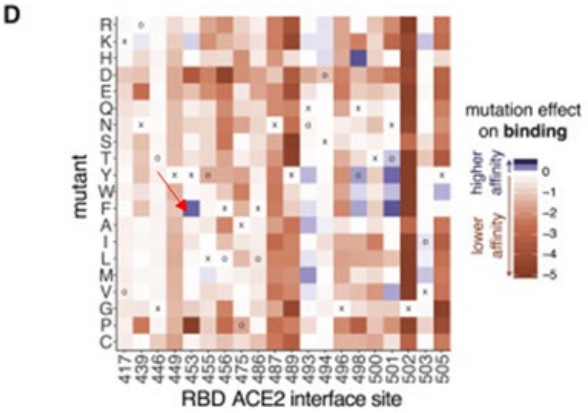
Several laboratories have infected ferrets with SARS-CoV-2 isolates. In an unrelated experimental infection study in ferrets at the Animal Plant Health Agency, UK (in collaboration with PHE Porton and funded by DEFRA) the Y453F mutation was detected in viruses shed in the respiratory tract from animals challenged with a 'human' virus. The study sought to evaluate the use of ferrets as a model for SARS-CoV-2 investigating clinical outcome, pathology, infection kinetics and associated immunity. Ferrets were subclinically infected and viral RNA was predominantly detected in the upper respiratory tract. Further, three respiratory tract samples from three animals at consensus level revealed the Y453F mutation in the spike gene. It appeared that the Y453F mutation that was observed in the study occurred *de novo* in the ferret and was not present in the initial inoculum (Everett et al unpublished/submitted). This is strong evidence that the mutation is selected to enable a functional interaction between virus Spike and mink ACE2.

Changes in spike in the receptor binding domain may also impact on its interaction with the human receptor. Put another way, as the virus adapts to mink, it may alter its ability to infect humans; mink adapted viruses may be more or less fit in humans.

Data on replication capacity of mink adapted viruses provided by Danish colleagues are currently unclear. They suggest on the one hand initial slow growth of cluster 5 variant in Vero cells but on the other a high titre reached of the same virus by 96 hours after infection. Replication in Vero cells is not a good indicator of replication in human airway.

The Y453F mink adapting mutation is shown in experimental systems to increase the Spike interaction with human ACE2.

Experiments performed at the Fred Hutchinson Institute in Washington USA, have already probed whether there are putative mutants that increase the interaction between spike and human ACE2. Y435F was discovered in this screen to significantly increase spike binding to human ACE2 (Figure 2 below taken from Starr et al Science. 2020).
https://www.sciencedirect.com/science/article/pii/S0092867420310035



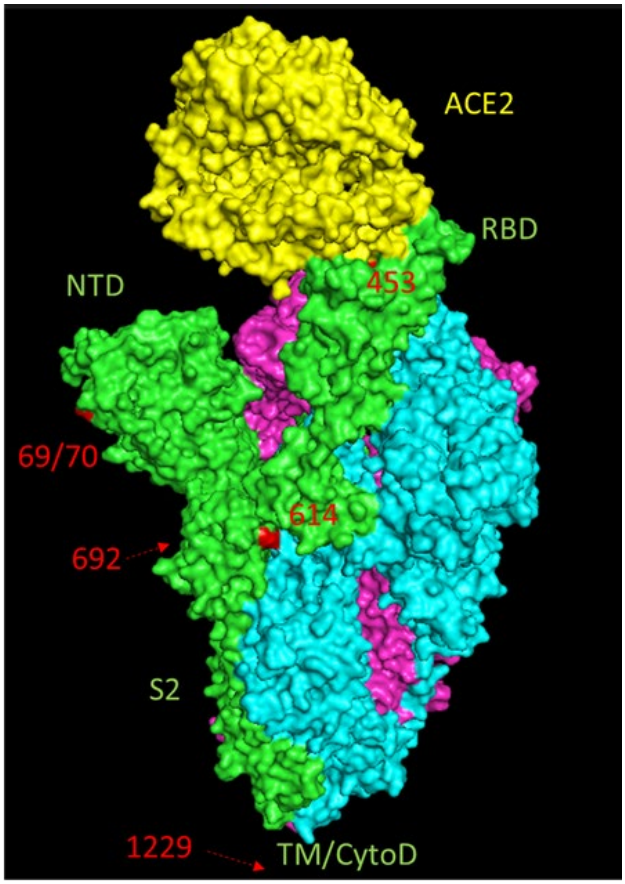
Thus the Y453F mutant might be expected to be fitter in humans, since it binds the receptor better. However these experiments were performed using a baseline spike protein derived from an early SARS CoV2 strain with the motif D614. Recent strains already possess increased affinity for human ACE2 conferred by the 614G mutation, and it possible that the addition of Y453F now makes little difference to the interaction that is already close to optimal. Indeed sequence analyses illustrate that of two mink outbreaks reported in the Netherlands, one that had D614 selected for Y453F whereas the other that had 614G did not. However the recent outbreaks on Danish mink farms have the D614G mutation and yet still selected for Y435F, so at least in mink these two mutations appear to be additive. We do not have data about how the Y453F mutation will affect Spike binding to human ACE2 when coupled with D614G.

Other mutations in spike of mink adapted viruses outside the RBD might also impact virus fitness

The cluster 5 Danish mink adapted viruses also carry a deletion in the spike glycoprotein at amino acids 69 and 70. Viruses that have both Y453F and the 69/70 deletion continue to be isolated from humans in Denmark. Interestingly this 69/70 deletion is also present in viruses that carry another RBD change in spike that has arisen independent and in humans, N439K. It is possible that the 69/70 deletion compensates for the RBD changes or enhances transmission of viruses that carry them.

The location of the 69/70 deletion is on a different part of Spike called the N terminal domain, and the functional consequence of the deletion is not clear at present. Figure 4 also shows the location of the other cluster 5 mutations on spike.

692 is close to the furin cleave site, and the 1229 is in the transmembrane region.



Without performing controlled experiments, we cannot know that the spike variants selected through growing in mink will impair or enhance the interaction of spike with human ACE2 and how this will impact on virus fitness in humans. Experiments should:

1. Compare the entry of viruses with the different Spike mutations into cells that have the mink or the human ACE2 receptor
2. Measure how well the mink-adapted virus replicates in (primary) human airway cells in comparison to the current circulating SARS Cov2 human strains.

The mink adapted cluster 5 virus is reported to evade neutralization by antibodies in human convalescent serum.

Even if the mink adaptations do not affect the transmission or replication fitness of SARS Cov2 in naive humans, they might alter the way the virus is seen by the immune system. For example mutations in the Spike receptor binding site might impact on how efficiently antibodies can neutralize the virus. Indeed, the Danish group who have isolated the cluster 5 virus report that this virus is less well neutralized by human convalescent serum. In their report https://files.ssi.dk/Mink-cluster-5-short-report_AFO2 they state that, of 9 convalescent sera they analysed, 2 showed a 4 fold or greater decrease in ability to neutralize the cluster 5 isolate compared to other human isolates that don't have the mink adapting mutations.

However, there are several technical issues in performing live virus neutralization assays to compare neutralization of different viruses by the sera or individual antibodies. If one virus grows at a

different rate than another, the quantification of the virus input to the assay can be difficult and then different challenge doses can contribute to misleading results. Currently, different platforms are being used around the world for this type of assay and there is an urgent need for standardization.

Since it is likely that Y453F mutation increases the affinity of interaction between spike and human ACE2, this decrease in antibody neutralization is not surprising. If the affinity of the spike:ACE2 interaction is higher, then more antibody will be required to neutralize. This is a known mechanism for antibody escape by influenza virus (Hensley et al. Science. 2009) https://science.sciencemag.org/content/sci/326/5953/734.full.pdf

Spike mutations are being reported by other groups, some of which also show decreased susceptibility to neutralization by monoclonal antibodies and convalescent sera

A number of publications are beginning to describe that SARS-CoV-2 has diversified as it has transmitted in humans. Mutations are present especially in Spike protein giving rise to 1,133 amino acids changes, including 171 in RBD. The most well know of these is the D614G change that affect the presentation of RBD and is now predominant. This change does to appear to have affected the antigenicity of the virus. Other mutations do affect the binding of antibodies to spike. The impact of naturally occurring mutations in spike on virus infectivity and antigenicity was first reported by Li et al (Cell 2020). More recently Liu et al have posted a preprint https://www.biorxiv.org/content/10.1101/2020.11.06.372037v1 describing spike mutations that attenuate monoclonal antibody and serum neutralization. One mutation at S477N was seen with high frequency in human virus sequences. The preprint from Thomson et al. https://www.biorxiv.org/content/10.1101/2020.11.04.355842v1 describes how the mutations at N439K also evades antibody neutralization and as stated above is now widespread on conjunction with the 69/70 deletion.

The mink adapted viruses and other viruses with spike mutations might have a fitness advantage in people with SARS-CoV-2 antibodies.

One possibility is that the mink adapting mutations or the other spike mutations that are being reported will then confer antigenic escape from antibodies raised against SARS-CoV-2 following infection or vaccination. Introduction of mink adapted viruses into humans as population immunity increases following a second wave might seed an antigenic escape variant- equally such variants might arise spontaneously in people who become re-infected as their own immunity wanes.

Informal reports from the SSI Denmark were reassuring in that rabbit sera raised to a candidate Spike based vaccine were still able to neutralize the cluster 5 variant. Nonetheless there is an urgent need to understand how each spike variant affects the potential efficacy of therapeutic monoclonal antibodies or vaccines.

Experiments should

1. Assess neutralization of live virus variants or pseudoviruses bearing spike variants by convalescent sera, monoclonal antibodies and sera from vaccines recipients.
2. Test for protection from infection or disease in animals that are pre-infected or immunized with wild type Spike virus or vaccines followed by challenge with viruses bearing Spike variants.

Surveillance programmes should be alert to the emergence of spike variants and a pipeline established to risk assess them for changes in antigenicity and fitness in human airway cells. Formal surveillance should also be considered for other animal sources of zoonotic transmission including domesticated and companion animals.

Implications for vaccine platforms

The plasticity in SARS CoV2 Spike sequence that is being observed as the virus continues to evolve raises the possibility that, as levels of natural and vaccine-induced immunity increase, virus mutants will be selected that evade antibody raised to the first wave strains. Therefore it is imperative that plans are put in place to monitor for this, and to update vaccines if necessary, as is done for influenza. This will require agile vaccine production platforms that can be rapidly updated to present antigen from contemporary strains, as well as a licensure arrangement similar to that in use for influenza that allows the updated product to be rolled out with limited testing rather than be treated as a new product. The possibility that multivalent vaccines might be required if SARS CoV2 diverges and co-circulates as several antigenically distinct lineages (as seen for the avian coronavirus IBV) should also be considered.