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ANIMAL GENETICS • REVIEW

The basis of mink susceptibility to SARS-CoV-2 infection

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Abstract
Of all known airborne diseases in the twenty-first century, coronavirus disease 19 (COVID-19) has the highest infection and death rate. Over the past few decades, animal origin viral diseases, notably those of bats-linked, have increased many folds in humans with cross-species transmissions noted and the ongoing COVID-19 pandemic has emphasized the importance of understanding the evolution of natural hosts in response to viral pathogens. Cross-species transmissions are possible due to the possession of the angiotensin-converting enzyme 2 (ACE2) receptor in animals. ACE2 recognition by SARS-CoV-2 is a critical determinant of the host range, interspecies transmission, and viral pathogenesis. Thus, the phenomenon of breaking the cross-species barrier is mainly associated with mutations in the receptor-binding domain (RBD) of the spike (S) protein that interacts with ACE2. In this review, we raise the issue of cross-species transmission based on sequence alignment of S protein. Based on previous reports and our observations, we can conclude that the occurrence of one of two mutations D614G or Y453F is sufficient for infection of minks by SARS-CoV-2 from humans. Unfortunately, D614G is observed in the world's most common line of virus B.1.1.7 and the latest SARS-CoV-2 variants B.1.617.1, B.1.617.2, and B.1.617.3 too.

Keywords Coronavirus · Cross-species infection · Minks · SARS-CoV-2 · Spike protein

Introduction

Coronaviridae family encompasses subfamily Coronavirinae subdivided into Alpha, Beta, Delta, and Gammacoronavirus genera, but only the first two genera can infect humans (Lu et al. 2015). SARS-CoV-2 belongs to the Betacoronavirus genera and causes COVID-19, which is now a great concerning issue all over the world (Rothan and Byrareddy 2020). The fatality rate of the disease varies between 1 and 10% causing severe health conditions, e.g., pneumonia, fatal myocardial injury, cardiac arrest, neurological damage, or kidney failure (Csiszar et al. 2020).

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Over the last two decades, three major coronavirus epidemics: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and the recent COVID-19, have occurred worldwide (Liu et al. 2021). Among all the airborne diseases of the twenty-first century, COVID-19 has the highest infection and death rate (Teruel et al. 2020). According to the WHO epidemiological report of 1st November 2021, the confirmed cases and deaths are 246,594,191 and 4,998,784, respectively (WHO 2021).

Bats are considered to be the likely source of coronavirus as the genomic sequence of SARS-CoV-2 is somehow similar to the coronaviruses found in the *Rhinolophus* bat (horseshoe bat) (Csiszar et al. 2020). Coronaviruses, being RNA viruses, exhibit a high mutation rate that allows them to adapt to a wide range of hosts (Cui et al. 2019). Besides humans, several mammals (African green monkey, cats, common marmosets, cynomolgus macaques, dogs, ferrets, fruit bats, hamsters, lions, rabbits, rhesus macaques, tigers, and tree shrew) can be affected by SARS-CoV-2 (Oude Munnink et al. 2021) and can have mild to the moderate clinical manifestations of the disease (Kostov 2020). Mammalian susceptibility to infection is due to the presence of the compatible ACE2 receptor (Banerjee et al. 2021)—a zinc-dependent peptidase, which plays an important role in blood pressure regulation through the renin-angiotensin pathway. ACE2 recognition by

SARS-CoV-2 is a critical determinant of the host range (Liu et al. 2020), interspecies transmission (Devaux et al. 2021), and viral pathogenesis (Wang et al. 2020a, b). Thus, the phenomenon of breaking the cross-species barrier is mainly associated with key amino acid mutations in the RBD of the S protein and the host ACE2 receptor (Dhama et al. 2020). Changes within the RBD may increase or decrease its affinity for the ACE2, directly affecting the ability of SARS-CoV-2 to enter the host cells (Burkholz et al. 2021).

Role of spike protein

SARS-CoV-2 is a single-stranded RNA virus with a positive polarity. Its genome size is about 30 kb and consists of 14 open-reading frames (ORFs) that encode 27 proteins (Yang and Rao 2021). The 5'-terminus of the SARS-CoV-2 genome contains ORF1a translated to pp1a polyprotein, which is proteolytically cleaved into 11 non-structural proteins (nsp1-11), and ORF1b translated to pp1ab polyprotein, which is proteolytically cleaved into five non-structural proteins (nsp12-16) (Yadav et al. 2021). Non-structural proteins play an essential role in viral replication and transcription. The 3'-end of the viral genome contains ORFs encoding structural proteins, known as the spike, envelope (E), matrix (M), and nucleocapsid (N) (V'kovski et al 2021). The S protein mediates receptor attachment and membrane fusion, the E protein promotes assembly and release of virions (Satarker and Nampoothiri 2020), and the M protein determines the shape of the coronavirus (Schoeman and Fielding 2019). Together, these three proteins form the viral capsid, while the N protein binds to the RNA of SARS-CoV-2, forming the ribonucleotide core (Dai and Gao 2021). Apart from above-mentioned structural proteins, there are eight accessory proteins (3a, 3b, 6, 7a, 7b, 8a, 8b, and 9b). However, they do not affect coronavirus replication but may contribute to the virulence of SARS-CoV-2 (Liu et al. 2014) (Fig. 1).

The SARS-CoV-2 S protein has a size of ~ 180–200 kDa with a total length of 1273 amino acids and consists of two subunits: S1 and S2. The S1 subunit contains the N-terminal domain (NTD) and the C-terminal domain (CTD). CTD functions as the RBD and is responsible for the SARS-CoV-2 tropism. The S2 subunit is comprised of the fusion peptide (FP), heptapeptide repeat sequence 1 (HR1), heptapeptide repeat sequence 2 (HR2), transmembrane domain (TM), and cytoplasmic domain (CT), which are related to coronavirus-host cell membrane fusion (Huang et al. 2020) (Fig. 2). Generally, the S protein occurs in a metastable conformation and the S1 and S2 subunits of the S protein remain non-covalently linked together (Wang et al. 2020a, b).

When the RBD successfully binds with the ACE2, various proteases like transmembrane protease serine 2 (TMPRSS2), cathepsin B, and cathepsin L promote the entry of SARS-CoV-2 into host cells through activation of the S protein by its proteolytic cleaving into S1 and S2 subunits (Huang et al. 2020). This cleavage takes place at

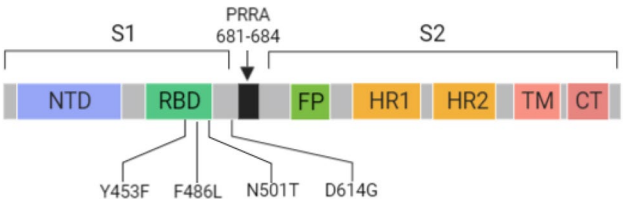

Fig. 2 SARS-CoV-2 S protein structure with mutations which were expected to be crucial for SARS-CoV-2 infection in minks (BioRender 2021a). Abbreviations stand for: CT, cytoplasmic domain; D614G, mutation in the S protein; F486L, mutation in the S protein; FP, fusion peptide; HR1, heptapeptide repeat sequence 1; HR2, heptapeptide repeat sequence 2; N501T, mutation in the S protein; NDT, N-terminal domain; PRRA, polybasic cleavage site; RBD, receptor-binding domain; S1, S1 subunit of the S protein; S2, S2 subunit of the S protein; TM, transmembrane domain; Y453F, mutation in the S protein

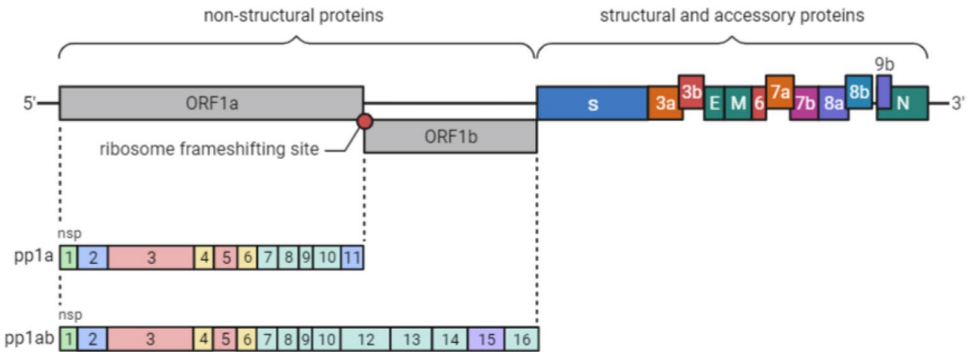

Fig. 1 SARS-CoV-2 genome structure (BioRender 2021b). Square descriptions: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, non-structural proteins; 3a, 3b, 6, 7a, 7b, 8a, 8b, 9b, accessory proteins; E, envelope protein; M, matrix protein; N, nucleocapsid protein; nsp, non-structural protein; ORF1a, open-reading frame 1a; ORF1b, open-reading frame 1b; pp1a, pp1a polyprotein; pp1ab, pp1ab polyprotein; S, spike protein

the junction of S1 and S2 subunits in a polybasic cleavage site (PRRA)—a significant determinant of SARS-CoV-2 transmission (Hu et al. 2021; Peacock et al. 2021), and subsequently at the S2' site in the S2 subunit. The S1 subunit dissociates, which enables conformational modification of the S2 subunit allowing SARS-CoV-2 membrane fusion (Dai and Gao 2021) or penetration through endocytosis and releasing the genome into the cytoplasm. The next stage of coronavirus replication is the translation of the ORF1a and ORF1b. It leads to the formation of pp1a and pp1ab polyproteins that are cleaved into 16 nonstructural proteins forming the replication-transcription complex (RTC) (V'kovski et al 2021). RTC is responsible for RNA replication and the transcription of subgenomic mRNAs serving as a template for the synthesis of structural proteins S, E, and M incorporated into the endoplasmic reticulum (ER) and the N protein, which forms a nucleocapsid with RNA. The formed nucleocapsid moves with the rest of the structural proteins to the endoplasmic reticulum-Golgi intermediate Compartment (ERGIC), where the maturation process, vesicle transport, and the release of progeny virions by exocytosis are initiated (Arya et al. 2021) (Fig. 3).

It has been observed that the transmission of SARS-CoV-2 from vertebrate animals to humans is possible in some situations. The first case of this kind of phenomenon defined as "zoonotic spillover" was reported in mink farms in the Netherlands (Dhama et al. 2020). COVID-19 cases were reported among farmworkers in the Netherlands and Denmark before infections in mink were discovered, suggesting that the animals were infected by humans (Oude Munnink et al. 2021). The potential of SARS-CoV-2 to jump across the species barrier should be carefully examined as many animals have an asymptomatic infection, which is challenging to detect (Kumar et al. 2021). Recent studies have revealed that a modification of the RBD structure is needed for SARS-CoV-2 to bind the ACE2 (Zhang et al. 2021). The RBD is the most changeable part of the genome of SARS-CoV-2 (Leroy

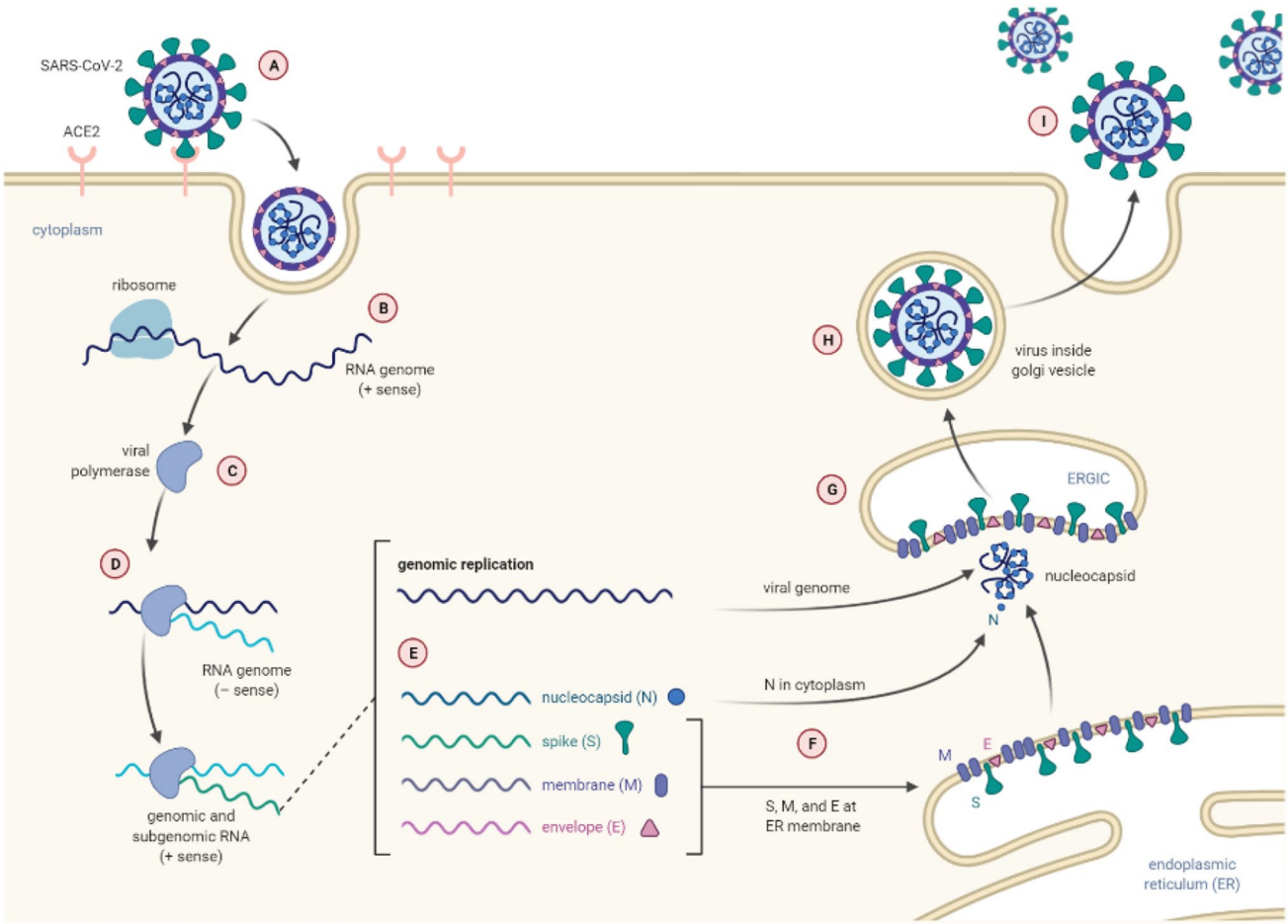

Fig. 3 SARS-CoV-2 replication cycle based on Reis et al. (2021). A—receptor binding and entry of SARS-CoV-2 via membrane fusion or endocytosis, B—release of viral genome, C—translation of viral polymerase protein, D—RNA replication, E—subgenomic (nested) transcription, F—translation of viral structural proteins, G—S, E, and M proteins combine with nucleocapsid, H—formation of mature virion, I—exocytosis of SARS-CoV-2

et al. 2020). The change of only 2–4 amino acids in the RBD can cause even 1000-fold differences in binding affinity to ACE2 (Holmes 2005). However, RBD/ACE2 interactions may occur even with comparatively significant alterations within the ACE2. The inability of the ACE2 of some species to function as a SARS-CoV-2 receptor is likely due to a combination of different kinds of mutations (Lu et al. 2015). In the absence of ACE2, several receptors named tyrosine-protein kinase receptor UFO (Axl), low-density lipoprotein receptor class A domain-containing protein 3 (LDLRAD3), and C-type lectin domain family 4 member G (CLEC4G) were shown to enable SARS-CoV-2 infection by binding to the NTD of its S protein (Baggen et al. 2021).

Spike protein mutations

From the point of cross-species SARS-CoV-2 infection, mutations within S protein appear to be the most relevant. The structure of the SARS-CoV-2 S protein can be modified by the genetic events that occur in zoonotic coronaviruses (Ellis et al. 2021). Analysis of SARS-CoV-2 S protein sequences from humans of all continents, compared with the original reference human SARS-CoV-2 S protein sequence from Wuhan-Hu-1, showed that 8155 out of 10,333 of them had at least one mutation. In total, 9654 mutations were detected corresponding to 400 different mutation sites. The mutation sites were distributed along the entire length of the S protein sequence with the highest mutation density near the protease cleavage site—between residues 675 and 692. The RBD included 44 mutation sites, in which the S77N, V483A, A344S, and N501Y mutations were the most frequent, while the Y453, G476, F486, T500, and N501 mutations were close to the ACE2 (Guruprasad 2021). Within the RBD, one of the very common mutations is the N439K substitution. Thomson et al (2021) demonstrated that the N439K mutation increases RBD affinity for the ACE2. However, viruses with this type of mutation have comparable replication capacity in vitro and cause infections similar in clinical effects to the wild-type. Nowadays, a SARS-CoV-2 amino acid change, D614G, is considered as dominant as this variant has more potential to neutralize antibodies, which may be relevant for vaccine development (Thomson et al 2021). The D614G mutation promotes an open conformation of the S protein, resulting in enhanced infectivity in human cells (Mansbach et al. 2021). Although this mutation is not localized inside the RBD, its effect on RBD could not be excluded due to the possible impact on the shape of the three-dimensional structure of the S protein.

The appearance of the N amino acid in the 501 positions is believed to be a key to human infection. The D501N mutation was found in the SARS-CoV-2 S protein sequence from Wuhan-Hu-1 (NC_045512), suggesting that it comes from the bat coronavirus RaTG13 (MN996532). The D501N mutation of RaTG13 RBD was shown to cause a significant increase (almost ninefold) in the binding strength with ACE2 among other mutations with increased ACE2 binding and SARS-CoV-2 transmission efficiency. Also, studies on the RaTG13 RBD double-site mutants showing a better affinity for the ACE2 than wild-type RBD confirmed that position 501 is one of the crucial sites responsible for different binding strengths of ACE2 to RaTG13 and SARS-CoV-2 RBDs (Zhang et al. 2021).

Further, the N501T mutation was observed in minks from the Netherlands. In the mouse model, the N501Y mutation has been associated with increased infectivity and virulence of SARS-CoV-2 (Gu et al. 2020). Nowadays, the N501Y mutation characterizes the novel SARS-CoV-2 variant from the UK named VOC202012/01 (B.1.1.7) (European Centre for Disease Prevention and Control 2021b), which was recently detected in Poland (Hryhorowicz et al. 2021). Along with it other S protein mutations describing the British variant appeared: HV 69–70 deletion, Y144 deletion, A570D, P681H, T716I, S982A, and D1118H. Some of these mutations, such as the 69–70 deletion in combination with the N501Y variant, increase the transmissibility of SARS-CoV-2. Also, the P681H mutation has a significant biological function due to its presence near the furin cleavage site (Public

Table 1 SARS-CoV-2 S protein mutations and functions

Mutation	Function	Impact on human infection	Reference
Y453F	Viral evasion of the antibody response	Increases the binding affinity of the S protein to ACE2	Harvey et al (2021)
F486L	Decrease S protein stability	Increases the binding affinity of the S protein to ACE2	Ahamad et al. (2020), Sardar et al. (2020)
N501T	De-stabilization of the S protein	Increases the binding affinity of the S protein to ACE2	Ahamad et al. (2020)
D614G	Promotes SARS-CoV-2 transmission (has potential to neutralize antibodies)	Increases the efficiency of cellular entry for the virus	Daniloski et al. (2021), Mansbach et al. (2021), Zhang et al. (2020a, b)

Health England 2020). It is estimated that B.1.1.7 is up to 70% more infectious than the previously circulating strains of SARS-CoV-2 in the UK (European Centre for Disease Prevention and Control 2021a) (Table 1).

Mutations affecting the glycosylation of viral proteins can change the binding affinity of S protein with ACE2 (Teng et al. 2021). Glycosylation is a process in which sugar moieties are co-transnationally added to the protein and play a vital role in expanding the genome's potential (Jayaprakash and Surolia 2017). It is one of the most ubiquitous and versatile modifications of proteins and can be classified as N-, O-, and C-linked according to the acceptor amino acid binds to the sugar moiety. The host glycosylation machinery is crucial for glycosylation of viral envelope glycoproteins (Bagdonaite and Wandall 2018) and glycosylation is a key in SARS-CoV-2 infection. It is critical for the stability of viral proteins as in most viruses, glycans make a significant interaction with GBPs (such as C-type lectins) on the host surface. Glycans on the surface of the virus and host cell play a vital role in viral entry, proteolytic cleavage of viral proteins, and recognition and neutralization of the virus by the host immune system (Hernández et al. 2021). The SARS-CoV-2 S protein is highly glycosylated on 22 N-glycan sites and a number of O-glycosylation sites (Groves et al. 2021). Viral entry through membrane fusion is often mediated by specific N-glycan epitopes. For example, glycosylation at the sites N331 and N343 are crucial for viral infection (Li et al. 2020). Blocking N-glycan biosynthesis at the high mannose stage has less effect in spike-ACE2 binding and also while viruses not having N-glycan enter the host less efficiently (Yang et al. 2020). Researchers have found that glycans at sites N165 and N234 stabilize RBD "up" conformation and stimulate binding with ACE2 receptor, while deletion of those residues reduces the binding of S protein with human ACE2 because of a conformational shift of the RBD toward the "down" state (Casalino et al. 2020). Most of the mutations on N-linked glycosylation sites and O-linked glycosylation sites increase the S protein stability and facilitate ACE2 binding (Teng et al. 2021). However, there is no data available that any of the mutations, which were expected to be crucial for SARS-CoV-2 infection in minks (Y453F, F486L, N501T, and D614G), alter S protein glycosylation.

Cross-species SARS-CoV-2 transmission

The diversity of the coronavirus genome is determined by several features that simultaneously support the viral adaptation to a new host. RNA proof-reading activity associated with the 3'-5' exonuclease activity, efficient recombination frequencies up to 25% during mixed infection, discontinuous RNA transcription, and the capability of self-change as the largest RNA virus of 27–31 kb are examples of such characteristics, which also lead to the development of new virus strains (Bolles et al. 2011). RNA proof-reading activity of SARS-CoV-2 was demonstrated for non-structural protein 14 (nsp14), also known as ExoN. It increases the fidelity of RNA synthesis by correcting nucleotide insertion errors caused by nonstructural protein 12 (nsp12) (RdRp) (Pachetti et al. 2020), maintaining the integrity of the viral genome (V'kovski et al 2021). Like an RNA proof-reading activity, discontinuous transcription is a unique process among known RNA viruses. In this process, SARS-CoV-2 produces subgenomic mRNAs (sgmRNAs), which have a common 5' "leader" sequence ranging from 65 to 98 nucleotides. The presence of a "leader" sequence in each transcript protects SARS-CoV-2 mRNA molecules from cleavage by the nonstructural protein 1 (nsp1), ensuring the efficient accumulation of viral mRNAs and proteins during infection (Sola et al. 2015). Although this mechanism is not directly related to viral cross-transmission, it can result in a greater mutation frequency in SARS-CoV-2, which may lead to the virus's cross-transmission.

An outbreak of viral severe pneumonia in Wuhan appeared to be linked to exposure to a virus reservoir at the Huanan wholesale seafood market, suggesting a possible zoonosis (Mahdy et al. 2020). There is currently no evidence that a particular wild host is the virus reservoir (Mansbach et al. 2021). Results from studies to date indicate that 2019-nCoV has the most similar sequence with bat coronavirus (Zhang et al. 2021). More interestingly, there is homologous recombination within the S glycoprotein of 2019-nCoV, which may explain its interspecies transmission and limited spread from human to human (Ji et al. 2020). The amino-terminal domain of the S protein is significantly unique for different host receptors, though that cross-transmission happens because of RNA recombination, which can alter the tissue tropism and virus virulence (Holmes 2005). Currently, the virus's cross-transmission and human-to-human transmission are also dependent on two S protein-binding hotspots (hotspot 31Lys and hotspot 353Lys) on the ACE2 surface, with which different naturally mutated SARS-CoV receptor-binding motifs can interact (Shang et al. 2020).

Bat-to-human

In comparison to SARS-CoV, bat coronavirus RaTG13 and human SARS-CoV-2 Wuhan-Hu-1 show 97.5% and 89.2% amino acid sequence similarity for S protein and RBD, respectively. SARS-CoV-2 contains a four-residue motif (residues 482–485: Gly-Val-Glu-Gly) that alters the structure of the ACE2-binding ridge and facilitates greater affinity of the virus for the N-terminal helix of ACE2. It

has been proven that the same residue motif in bat RaTG13 can use human ACE2 as an entry receptor. Further, it provides evidence that SARS-CoV-2 may be the result of the evolution of RaTG13 or a RaTG13-related bat coronavirus. Also, the RaTG13 genome sequence has a 96.2% similarity with SARS-CoV-2. The L486F, Y493Q, and D501N residue changes from RaTG13 to SARS-CoV-2 may also be responsible for the transmission of SARS-CoV-2 to humans, as is the conservation of Leu455 between RaTG13 and SARS-CoV-2 (Shang et al. 2020; Zhang et al. 2021).

Two transmission routes of SARS-CoV-2 from bat to human are possible. It may be either by the direct transmission or transmission through an unknown intermediate host. The intermediate host for bat-to-human transmission has been considered to be pangolin. Malayan pangolin (*Manis javanica*) coronaviruses from Guangxi (GX) and Guangdong (GD) provinces in China show a close relationship with SARS-CoV-2. PCoV_GX and PCoV_GD show 85.5 to 92.4% sequence identity with SARS-CoV-2. Also, the S protein and RBD of PCoV_GX show 92.3% and 86.7% amino acid sequence similarity respectively with SARS-CoV-2, while PCoV_GD shows 89.6% and 96.9%, respectively (Zhang et al. 2021). PCoV_GD receptor-binding motif contains Leu455, the 482–485 loop, Phe486, Gln493, Asn501, and RBM of PCoV_GX has Leu455, the 482–485 loop, Leu486, Glu493, Thr501, which facilitate ACE2 recognition (Shang et al. 2020). However, further analysis proved that pangolins are no longer recognized as SARS-CoV-2 intermediate hosts (Xiao et al. 2021).

Human-to-mink

The SARS-CoV-2 sequences found in minks and humans show close similarity (Oreshkova et al. 2020). The human and mink ACE2 protein, showing high homology, has the peptide "353-KGDFR-357" located on the ACE2 surface, which binds to the S protein RBD (Sharun et al. 2021). In Denmark and the Netherlands, several cases of mink with the S protein Y453F mutation have been reported, but the strains from both countries did not belong to the same genetic clades (European Centre for Disease Prevention and Control 2020). The Y453F RBD mutation can be considered as an adaptation to the mink ACE2, which may increase affinity for human ACE2 (Bayarri-Olmos et al. 2021). Along with the Y453F mutation, three other mutations have been identified: 69-70delHV, I692V, and M1229I (European Centre for Disease Prevention and Control 2020). Five different clusters of different S protein mutations have been found in the Netherlands, including cluster 5, which is gaining increasing attention (Larsen 2020). Stray and feral cats near Dutch mink breeding areas have tested positive for SARS-CoV-2 indicating that they may be intermediate hosts for human-to-mink or mink-to-human transmission of the virus (Sharun et al. 2021). Welkers et al. (2021) has described that three substitutions (Y453F, F486L, and N501T) facilitate SARS-CoV-2 interaction with different residues of human and mink ACE2, which suggest that having one of these mutations will allow SARS-CoV-2 to infect both human and mink. Y453F substitution lets SARS-CoV-2 interact with the H34 residue of human ACE2 and the Y34 residue of mink ACE2. In the case of F486L substitution, the coronavirus interrelates L79, M82, Y83, and H79, T82, Y83 residues of human and mink ACE2, respectively. Also, SARS-CoV-2 can interact with Y41, K353, G354 residues of human ACE2 and Y41, K353, R354 of mink ACE2 when it has N501T substitution (Welkers et al. 2021).

Human-to-other animals

Coronavirus has the potential for cross-species transmission and has a strong history of host switching (Bolles et al. 2011). The disease can be considered as a zoonotic spillover as the 1st patient was associated with the Huanan wholesale seafood market in China where various wildlife species were traded (Mahdy et al. 2020). In principle, SARS-CoV-2 infection in various animal species has been reported since then. All mammals possess the ACE2 and can be infected by SARS-CoV-2 as the RBD of the coronavirus has significant potential to bind to ACE2. Cats are such animals and during the SARS-CoV-2 outbreak in Wuhan, 15 out of 102 cats (14.7%) tested positive but they were in normal condition (Zhang et al. 2020a, b). SARS-CoV-2 RNA was also found in cats' feces and gastric fluids (Leroy et al. 2020).

The first case of pet dog infection was reported in Hong Kong (Costagliola et al. 2020). Dog serological screening (Pomeranian Loulou) revealed SARS-CoV-2 antibodies in the blood whose owner was also infected by the coronavirus. SARS-CoV-2 was also found in a German shepherd and its owner, and sequencing confirmed that the dog was directly infected by a human (Leroy et al. 2020).

Experimental studies on a group of 9 dairy calves have shown that 2 out of 6 inoculated animals were positive but their susceptibility to SARS-CoV-2 infection was low (Ulrich et al. 2020).

Evidence has shown that several non-domestic animals are also susceptible to SARS-CoV-2 infection. Tigers (*Panthera tigris*) and lions (*Panthera leo*) were reported to be naturally infected by SARS-CoV-2 at Bronx Zoo, New York, and the sequence data of tigers and zookeepers shows 6 single nucleotide polymorphisms compared to the Wuhan-Hu-1 sequence (NC_045512) (McAloose et al. 2020). Gorillas at the San Diego Safari Zoo Park (CA, USA) were also reported to be positive for COVID-19.

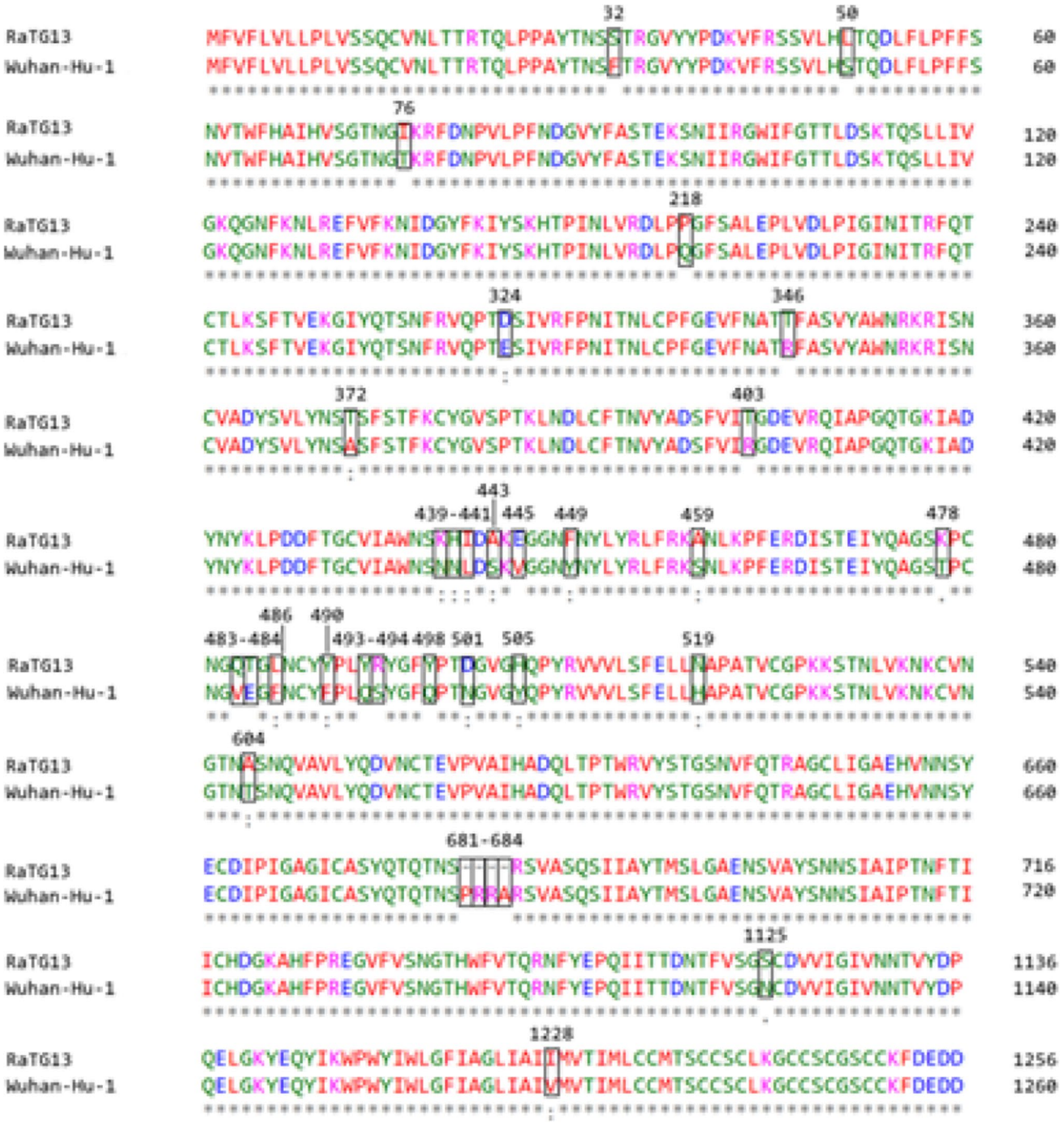

Fig. 4 Alignment of the SARS-CoV-2 S protein sequence from Wuhan-Hu-1 and bat coronavirus RaTG13 using Clustal Omega bioinformatics tool (EMBL-EBI 2021). Boxes indicate substitutions (S32F, L50S, I76T, P218Q, D324E, T346R, T372A, T403R, K439N, H440N, I441L, A443S, E445V, F449Y, A459S, K478T, Q483V, T484E, L486F, Y490F, Y493Q, R494S, Y498Q, D501N, H505Y, N519H, A604T, S1125N, and I1228V) present in the compared genomes

From the feces sample of 8 gorillas, 3 were tested positive (UNESCO 2021). Evidence has found that pigs and several poultry species including chickens, turkeys, ducks, geese, and Japanese quail are safe from SARS-CoV-2 infection (Mahdy et al. 2020). Also, the oropharyngeal swab sample tested by RT-qPCR assay from rabbit and guinea pig owned by COVID-19 patients resulted negative for SARS-CoV-2 (Ruiz-Arrondo et al. 2021).

Analysis

Bat-to-human

SARS-CoV-2 S protein sequence from Wuhan-Hu-1 (NC_045512) was compared to the S protein sequence obtained from the bat coronavirus RaTG13 (MN996532) using the Clustal Omega bioinformatics tool (EMBL-EBI 2021), which was shown in Fig. 4. Alignment analysis revealed the presence of 29 substitutions that led to the SARS-CoV-2 transmission from bat to human. The most common mutations were threonine to arginine, alanine to serine, and tyrosine to glutamine mutations. Also, four insertions were detected in the Wuhan-Hu-1 S protein sequence

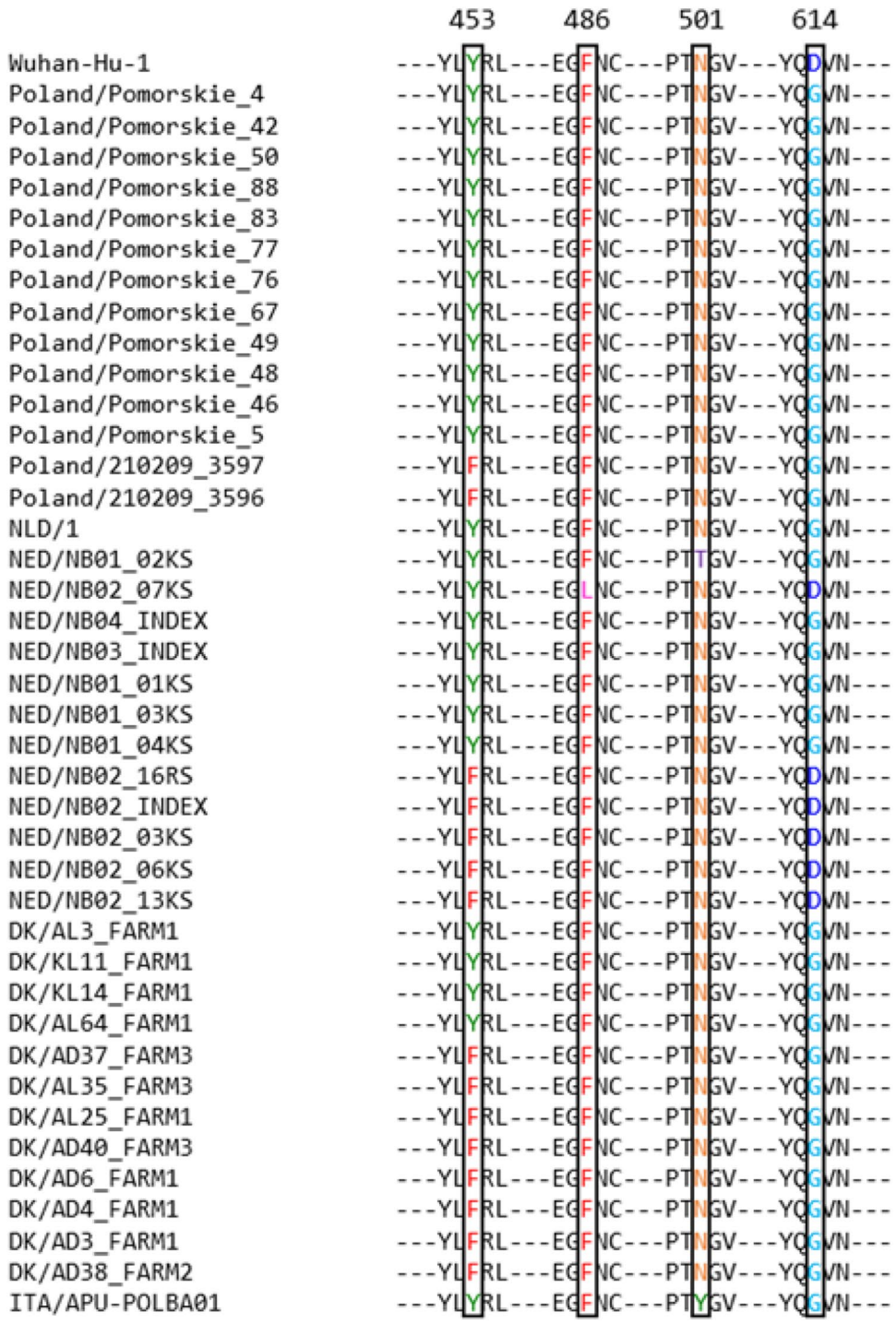

Fig. 5 Alignment of the SARS-CoV-2 S protein sequence from the reference Wuhan-Hu-1, human SARS-CoV-2 variant B.1.1.7 (ITA/APU-POLBA01) and mink coronavirus from the Netherlands (NLD and NED), Denmark (DK), and Poland. 453, 486, 501, 614, mutation sites in the S protein sequences; D, aspartic acid; F, phenylalanine; G, glycine; L, leucine; N, asparagine; T, threonine; Y, valine

in positions 681–684 (Pro-Arg-Arg-Ala) (polybasic cleavage site).

Human-to-mink

We compared the SARS-CoV-2 S protein sequence from Wuhan-Hu-1 (NC_045512) with mink sequences from the Netherlands and Denmark (GenBank) and Poland (GISAID) using the bioinformatics tool Clustal Omega (EMBL-EBI 2021), as shown in Fig. 5. These sequences were further aligned with the S protein sequence from the new UK SARS-CoV-2 variant B.1.1.7 (sequence ITA/APU-POLBA01) (MW450666). Alignment analysis indicated the presence of three main substitutions—Y453F, F486L, and N501T, which were expected to be crucial for SARS-CoV-2 infection in minks according to Welkers et al. (2021). The Y453F mutation was detected in 5 out of 13 mink coronavirus isolates from the Netherlands, in 8 out of 12 mink coronavirus isolates from Denmark, and in 2 out of 14 mink coronavirus isolates from Poland. The F486L mutation was observed in only one mink coronavirus isolate from the Netherlands; however, it was not observed in mink coronavirus isolates from Denmark and Poland. The N501T mutation was found in only one mink coronavirus isolate from the Netherlands; however, it was not detected in mink coronavirus isolates from Denmark and Poland. None of the mink coronaviruses isolates from the Netherlands, Denmark, and Poland had two or three of these mutations simultaneously. In 22 cases, none of the mutations described by Welkers et al. (2021) was observed. However, in all of these cases, we have noticed substitution D > G at position 614. The D614G mutation was present together with the Y453F mutation in 10 mink coronavirus isolates from Denmark and 2 mink coronavirus isolates from Poland. The Y453F, F486L, and N501T mutations were not found in the SARS-CoV-2 variant B.1.1.7, but the D614G mutation was present.

Discussion

Spike glycoprotein mediates cell adhesion and is the primary target of neutralizing antibodies (Dai and Gao 2021). SARS-CoV-2, like other RNA viruses, has a high mutation ability (Lauring and Hodcroft. 2021), which is a great obstacle in developing vaccines against this virus. The SARS RBD is heterogeneous, with specified sequence variation at key residues, which facilitates the cross-transmission of the virus among the species and also has an influence on host immune response (Bolles et al. 2011). Several non-human species infected by the SARS-CoV-2 have been reported by different sources. Last year, COVID-19 became a danger for mink farming in many countries, including Denmark and the Netherlands. Millions of minks have been culled just to prevent the emergence of vaccine-resistant variants (Dyer 2020; Oreshkova et al. 2020). Welkers et al. (2021) have shown that multiple ACE2 residues that differ between human and mink ACE2 interact with the Y453F, F486L, or N501T residues. This can be a crucial reason for the transmission of SARS-CoV-2 between minks and humans.

Ul-Rahman et al. (2020) has done phylogenetic and comparative residue analysis of SARS-CoV-2 strain (MN908947; Wuhan-Hu-1) and a wide range of non-human mammalian species including mink and found maximum genetic homology among dog-, cat-, tiger-, mink-, mouse-, bat-, and pangolin-derived SARS-CoV-2 sequences. This study suggests that these strains may have come from one common ancestor by the positive selection and continuous evolution in different hosts. According to Welkers et al. (2021), each of the three mutations (Y453F, F486L, and N501T) results in SARS-CoV-2 infection in minks. During our analysis, we have found the F486L mutation in the RaTG13 sequence, but it was observed in only one of the minks, so it seems that this mutation has no essential role in mink infection. The Y453F and N501T mutations were not detected in the RaTG13 sequence, which suggests that this may be a change determining new interspecies infections.

Several mink-related SARS-CoV-2 strains have been found with different mutations. The S protein mutation Y453F has been observed in minks from Denmark and the Netherlands. Also, mink-associated strains from Denmark have a deletion of two amino acids (69–70) in the S protein (European Centre for Disease Prevention and Control 2020). Along with these, two other S protein mutations (I692V, M1229I) have been observed in the cluster's 5 variant strains (Larsen 2020). Substitution D614G, which is mainly common in humans, is also observed in coronavirus from mink (Hoffmann et al. 2021). An additional mutation H182Y within ORF3a was also found in mink sequences from Denmark (Hammer et al. 2021). Our short analysis turns new lights on—which mutations are important for cross-species infections. We have found two mutations—the Y453F and D614G, which are common in Western Europe and Poland and allow mink to become infected. During our analysis, we have observed the presence of the Y453F mutation in 5 out of 13 mink coronavirus isolates from the Netherlands, in 8 out of 12 mink coronavirus isolates from Denmark, and in 2 out of 14 mink coronavirus isolates from Poland. The D614G mutation was detected in 7 out of 13 mink coronavirus isolates from the Netherlands, 12 out of 12 mink coronavirus isolates from Denmark, and 14 out of 14 mink coronavirus isolates from Poland. From the point of view of the mink infection, the D614G mutation may be important because all minks from Denmark and Poland have this mutation. We can conclude that the occurrence of one of the two mutations—D614G or Y453F, is sufficient for the infection of minks by SARS-CoV-2 from humans. There was only one

strain from the Netherlands that does not have either Y453F or D614G but has the F486L mutation.

Now in Poland, almost 90% of the SARS-CoV-2 infection is done by the novel SARS-CoV-2 UK variant B.1.1.7 (Instytut Genetyki Człowieka Polskiej Akademii Nauk 2021). Because of the current pandemic status of SARS-CoV-2 worldwide including Poland and the threat of the most common UK strain B.1.1.7, we decided to answer the question: Is this strain a threat to mink farms in Poland and worldwide? Unfortunately, the D614G is observed in the UK SARS-CoV-2 B.1.1.7 variant. However, in all sequences stored in GISAD from Polish minks, three mutations were present: G75V, D614G, and C1247F. If any modification of the S protein is needed to infect minks in Poland, one of them (G75V, D614G, and C1247F) enables such infection, and out of these three mutations, only one—the D614G—was observed in the B.1.1.7 variant. What is worse, this variant makes the coronavirus more infectious and has the highest potential to neutralize antibodies which can have a major impact on vaccine efficacy (Thomson et al 2021). In addition, the latest SARS-CoV-2 variants that were first reported in India: B.1.617.1, B.1.617.2, and B.1.617.3 have also the D614G mutation (European Centre for Disease Prevention and Control 2021a, b).

Animal reservoirs and intermediate hosts of SARS-CoV-2 should be identified to stop or reduce the chances of zoonotic transmission to humans (Liu et al. 2020). As a higher mutation rate reveals the zoonotic nature of the SARS-CoV-2 virus and the COVID-19 pandemic has the highest number of global deaths in this century, more studies should be focused on other undetected members from the Coronaviridae family, which can also be a reason for a future pandemic.

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