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BINDING VARIABILITY OF ANIMALS TO SARS-COV-2 SPIKE PROTEIN

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ABSTRACT: The aim of this study was to compare polymorphic regions of the angiotensin converting enzyme 2 (ACE2) receptor that are known to affect the susceptibility to SARS-CoV-2 in a number of different vertebrates. The amino acid sequences of a ligand-binding domain of the ACE2 receptor of animals known to be susceptible to contracting SARS-CoV-2 were compared those animals that are thought to be unlikely to contract that virus. Polymorphic regions can be successfully identified to predict which animals might be more likely to be infected by the SARS-CoV-2 virus and highlight possible further complications SARS-CoV-2 could have on society through the meat, fur and pet industries. Animals that play a key role in the pet and meat industry such as cows, pigs, chickens, cats, sheep, horses, rabbits and dogs, as well as other animals that are closely related to humans such as common chimpanzees (*Pan troglodytes*) and Sumatran orangutans (*Pongo abelii*) were included to aid an effective comparison between these dissimilar animals. Differences in the amino acid sequences of the ligand-binding domain were identified using protein sequencing alignment tools. The number of specific amino acids known to be required for successful binding along the ACE2 receptor varied among the animals used in this study hence raising issues regarding the possible susceptibility of particular domesticated animals to contract the SARS-CoV-2 virus which are discussed later on.

Keywords: animal, bioinformatics, coronavirus, ligand, polymorphisms.

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1.INTRODUCTION

Both severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) bind to the angiotensin converting enzyme 2 (ACE2) receptor to gain entry to cells [1,2]. A strong affinity between the SARS-CoV receptor binding (RBM) and the ACE2 human receptor are essential for efficient entry, however occasional polymorphisms can occur along the ligand-binding domain of the ACE2 receptor, that can weaken binding affinity and thereby reduce susceptibility to infection [3,4,5]. Shi and colleagues [6] demonstrated that polymorphisms within the ligand-binding domain of the ACE2 receptor in pigs, chickens and dogs [6,7,8] resulting in a weaker interaction with the SARS-CoV-2 RBM whilst there is a stronger interaction between the ACE2 receptor and the SARS-CoV-2 RBM in humans, chimpanzees and cats [6].The primary objective of this study was to compare the ACE2 receptor ligand binding domain of additional animals (wild, domesticated and livestock) and compare them to animals with known susceptibilities to the virus such as chimpanzees, Sumatran orangutans, cats and humans. In this way species susceptibility to the SARS-CoV-2 virus can be predicted.

2. MATERIALS AND METHODS

The protein sequence of the ligand-binding domain of ACE2 receptor was obtained using a previously published source [9]. BlastP was utilized to align the ACE2 receptor protein sequences of humans (Homo Sapiens, common chimpanzees (Pan troglodytes), Sumatran orangutans (*Pongo abelii*), cats (*Felis catus*), pigs (*Sus scrofa domesticus*), chickens (*Gallus gallus domesticus*), dogs (*Canis lupus familiaris*), cows (*Bos taurus*), sheep (*Ovis aries*), rabbits (*Oryctolagus cuniculus*) and horses (*Equus caballus*). Protein sequences of these animals were obtained from UnitProt.org. Once the protein sequences were aligned, the coordinates of the ligand-binding domain were identified [9]. The amino acids known to contribute to binding affinity in all of the animals were highlighted which identified any major polymorphic regions along the ACE2 ligand binding domain [10].

Table 1: Amino acids known to contribute to binding affinity [4] between the ACE2 receptor and the SARS-CoV-2 spike.

Amino acid along ACE2 receptor known to contribute to binding affinity	SARS-CoV-2 spike
Asn90	Arg408
Ser19	Arg487
Gln24	Ala475
Met82	Phe486
Leu79	Phe486
Tyr83	Phe486
Glu329	Arg439

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Amino acid along ACE2 receptor known to contribute to binding affinity cont.	**SARS-CoV-2 spike cont.**
Lys31	Leu455
Lys31	Gln493
Glu35	Gln493
Lys353	Asn501

3. RESULTS AND DISCUSSION

Using UniProt.org, the ACE2 receptor was shown to consist of 805 amino acids in all the animals studied. BLAST sequencing identified polymorphisms within the ACE2 receptor sequence (Figure 1).

Table 2: Amino acids present at the coordinates along the ACE2 ligand-binding motif. The amino acids in bold are different to the amino acids necessary for binding with the SARS-CoV-2 receptor binding motif.

Animals	**Amino acid**										
	19	**24**	**31**	**35**	**38**	**79**	**82**	**83**	**90**	**329**	**353**
Chimpanzee	Ser	Gln	Lys	Glu	Asp	Leu	Met	Tyr	Asn	Glu	Lys
Human	Ser	Gln	Lys	Glu	Asp	Leu	Met	Tyr	Asn	Glu	Lys
Sumatran Orangutan	Ser	Gln	Lys	Glu	Asp	Leu	Met	Tyr	Asn	Glu	Lys
Cat	Ser	**Leu**	Lys	Glu	**Glu**	Leu	**Thr**	Tyr	Asn	Glu	Lys
Rabbit	Ser	**Leu**	Lys	Glu	Asp	Leu	**Thr**	Tyr	Asn	Glu	Lys
Dog	Ser	**Leu**	Lys	Glu	**Glu**	Leu	**Thr**	Tyr	**Asp**	Glu	Lys
Pig	Ser	**Leu**	Lys	Glu	Asp	**Ile**	**Thr**	Tyr	**Thr**	**Asn**	Lys
Chicken	**Asp**	Glu	Lys	**Arg**	Asp	**Asn**	**Arg**	**Phe**	**Asp**	**Thr**	Lys
Cow	Ser	Gln	Lys	Glu	Asp	**Met**	**Thr**	Tyr	Asn	**Asp**	Lys
Sheep	Ser	Gln	Lys	Glu	Asp	**Met**	**Thr**	Tyr	Asn	**Asp**	Lys
Horse	Ser	**Leu**	Lys	Glu	**Glu**	Leu	**Thr**	Tyr	Asn	Glu	Lys

The strength of the binding between the ligand-binding domain of the ACE2 receptor and the SARS-CoV-2 RBD in dogs, cows, cats, sheep, horses and rabbits is more questionable; although these animals share many amino acids required for successful binding, not all the amino acids are present

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and therefore this could potentially reduce their susceptibility to contract the virus [11]. This research is important as it may provide a way of predicting which animals are more susceptible to contraction of SARS-CoV-2 and the potential impacts this virus may have on the meat, pet and fur industries. For example, if cows and sheep are susceptible to contracting the SARS-CoV-2 virus this could greatly influence meat production. Of the other species studied in the study, the rabbit, having 9 of the amino acids that conferred a successful bind (Table 2), may also be susceptible to SARS-CoV-2 and indeed it has been recently shown that rabbits are susceptible to COVID [12,13,14]. Although the infection was shown to be asymptomatic this could have a potential impact on the meat and fur industries as well as domesticated pets, and shows the importance of supporting the meat and fur industry through additional protections to ensure that an evident decline in the populations of livestock does not occur [15].

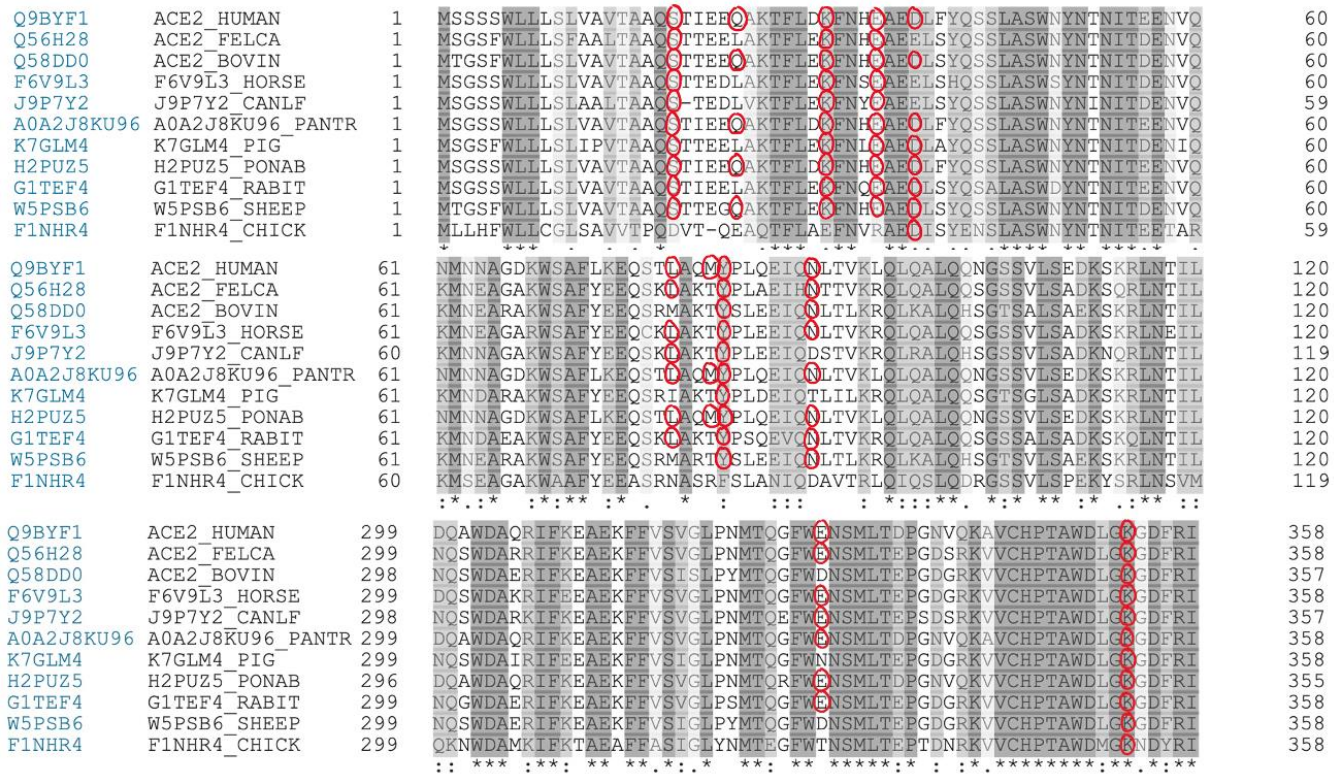

Figure 1. BLAST sequence alignment of the ACE2 receptor from human, cat, cow, horse, dog, chimpanzee, pig, Sumatran orangutan, rabbit, sheep and chicken. The amino acids circled in red are the amino acids favourable for a successful binding to the SARS-CoV-2 receptor binding motif.

4. CONCLUSION

It is clearly evident that two primates in the study, Sumatran orangutans and chimpanzees, sharing the greatest number of favourable amino acids for a successful bind, are the most vulnerable to infection. For this reason, rehabilitation centres and nature reserves will need additional support in keeping these animals protected, and these species may benefit from immunization.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

Author has no conflict of interest.

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