



## Research Paper

## A survey of genetic variants in SARS-CoV-2 interacting domains of ACE2, TMPRSS2 and TLR3/7/8 across populations

In-Hee Lee<sup>a,1</sup>, Ji-Won Lee<sup>b,c,1</sup>, Sek Won Kong<sup>a,d,\*</sup><sup>a</sup> Computational Health Informatics Program, Boston Children's Hospital, Boston, MA 02115, USA<sup>b</sup> Department of Nephrology, Boston Children's Hospital, Boston, MA 02115, USA<sup>c</sup> Department of Pharmacology, Graduate School of Dental Medicine, Hokkaido University, Sapporo 060-8549, Japan<sup>d</sup> Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA

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## ABSTRACT

The COVID-19 pandemic highlighted healthcare disparities in multiple countries. As such morbidity and mortality vary significantly around the globe between populations and ethnic groups. Underlying medical conditions and environmental factors contribute higher incidence in some populations and a genetic predisposition may play a role for severe cases with respiratory failure. Here we investigated whether genetic variation in the key genes for viral entry to host cells—ACE2 and TMPRSS2—and sensing of viral genomic RNAs (i.e., TLR3/7/8) could explain the variation in incidence across diverse ethnic groups. Overall, these genes are under strong selection pressure and have very few nonsynonymous variants in all populations. Genetic determinant for the binding affinity between SARS-CoV-2 and ACE2 does not show significant difference between populations. Non-genetic factors are likely to contribute differential population characteristics affected by COVID-19. Nonetheless, a systematic mutagenesis study on the receptor binding domain of ACE2 is required to understand the difference in host-viral interaction across populations.

## 1. Introduction

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is a pandemic as of Mar. 2020. Initial reports from China revealed diverse risk factors, clinical courses and outcome for a relatively homogenous population (Zhou et al., 2020a). Morbidity and mortality vary between populations (Yancy, 2020). African Americans and Latinos are disproportionately affected by COVID-19 and show significantly higher mortality compared to the other race and ethnic groups in the US (Wadhera et al., 2020) and in the UK (Kirby, 2020). A “healthcare disparity” must be responsible for the high incidence among minorities although socioeconomic factors, underlying medical conditions, and the difference in genetic susceptibility to SARS-CoV-2 infection may contribute (Chen et al., 2020). Of note, a 3p21.31 gene cluster—*SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6* and *XCR1*—is associated with genetic susceptibility for severe COVID-19 cases with respiratory failure (Ellinghaus et al., 2020). To find allelic variation across populations in the genes that are known to be involved in viral entry to the host cells and sensing of viral RNA in host immune cells, we surveyed publicly available databases of genomic variants.

SARS-CoV-2 is an enveloped and positive single-stranded RNA (ssRNA) virus and initiates human cell entry by binding of spike (S) protein present on the viral envelope to angiotensin converting enzyme 2 (ACE2) receptor on the host cells (Zhou et al., 2020b). The SARS-CoV S protein/ACE2 interface has been elucidated at the atomic level, and the ACE2 was found to be a key factor of SARS-CoV transmission (Li et al., 2005b). The binding mode of SARS-CoV-2 receptor binding domain (RBD) to ACE2 is nearly identical to SARS-CoV (Lan et al., 2020). The S protein is cleaved into S1 and S2 by the type 2 transmembrane serine protease (TMPRSS2) and endosomal cysteine proteases cathepsin B and L (CatB/L) (Du et al., 2009). TMPRSS2 is believed to be of utmost importance for SARS-CoV-2 entry into host cells. Recent studies demonstrated that an inhibitor of the protease activity of TMPRSS2—camostat mesylate—attenuated SARS-CoV-2 entry into lung epithelial cells suggesting a promising candidate for potential intervention against COVID-19 (Hoffmann et al., 2020). The C-terminal domain of S1 subunit is responsible for binding of SARS-CoV-2 to ACE2 and the S2 subunit undergoes a conformational change that result in virus-membrane fusion and entry into the target cell (Du et al., 2009). Viral genomic RNA is then released and translated into viral polymerase

\* Corresponding author at: 401 Park Drive, LM5528.4, Boston, MA 02115, USA.

E-mail address: [sekwon.kong@childrens.harvard.edu](mailto:sekwon.kong@childrens.harvard.edu) (S.W. Kong).<sup>1</sup> Contributed equally.

proteins for viral replication. Innate immune response is the first line of host defense mechanism for SARS-CoV-2 infection. Toll-like receptors recognize the viral RNA – double-stranded RNA (dsRNA) by TLR3 and ssRNA by TLR7 and TLR8 – and trigger innate immune responses such as the expression of inflammatory genes for type I interferons and pro-inflammatory cytokines (Iwasaki and Pillai, 2014; Iwasaki and Yang, 2020).

Here we surveyed the genetic variants in functional residues of *ACE2*, *TMPRSS2*, *CTSB/L* (CatB/L), and *TLR3/7/8* to investigate the difference in the genetic predisposition to the susceptibility of SARS-CoV-2 infection and the initiation of innate immune response. For *ACE2*, we investigated genetic variants in the residues on the interface to SARS-CoV-2 RBD from recent structural analyses (Hussain et al., 2020; Lan et al., 2020; Shang et al., 2020; Wrapp et al., 2020; Yan et al., 2020). Given the high sequence similarity between S proteins of SARS-CoV-2 and SARS-CoV, we also investigated the residues shown to inhibit interactions from in vitro mutagenesis analysis (Li et al., 2005b). We checked two residues reported to cause loss of cleavage activity of *TMPRSS2* (Afar et al., 2001) and the enzymatically active sites for CatB/L. A total of 16 residues of TLR7 that are necessary for ssRNA-induced activation (Zhang et al., 2016) and the residues affecting reaction to ssRNAs from in vitro mutagenesis studies for TLR3 (Bell et al., 2006; de Bouteiller et al., 2005; Sarkar et al., 2007) and for TLR8 (Tanji et al., 2015) were checked for sequence variation. Additionally, we searched for nonsynonymous variants that would cause loss of gene function (i.e., frameshift, in-frame insertion/deletion, stop-gain, splice-disrupting, start-lost and stop-lost). The list of reported genetic variants in the genes and their allele frequencies (AFs) were compiled from three population-scale genomic variants databases—gnomAD (Karczewski et al., 2020), Korean Reference Genome Database (Jung et al., 2020), and TogoVar (a Japanese genetic variation database available at <https://togovar.biosciencedbc.jp/>)—and three whole-genome sequencing datasets (i.e., 1000 Genomes Project (Clarke et al., 2017), Genetissue Expression (Consortium et al., 2017), and Simons Genome Diversity Project (Mallick et al., 2016)).

*ACE2* is highly conserved with few nonsynonymous variants in the interacting domain with the SARS-CoV-2 RBM (Lan et al., 2020). Of 370 coding variants in *ACE2*, 248 were nonsynonymous variants with the highest AF of 1.6% (rs41303171). Within 33 residues interfacing the SARS-CoV-2 RBM, 19 variants (including 4 synonymous variants) were found with average AF of 0.03% (ranges 0–0.39%) (Table 1). Only one of the 19 variants (rs4646116; K26R) had global AF greater than 0.1% (AF = 0.39%). Rs4646116 (NC\_000023.10:g.15618958 T > C) had the largest AF difference across populations: the lowest AF (0.007%) in East Asian and the highest (0.59%) in Non-Finnish European. The impact of this variant is not yet investigated with structural analysis but was not classified as deleterious (of possible impact on the structure and function of the protein) by in silico prediction algorithms such as SIFT and Polyphen2. The other variants were either very rare (i.e., population AF < 0.1%) or unique to a population or two. For the five known residues—K31, E35, D38, M82 and K353—that were reported to significantly change binding affinity to viral S protein (Li et al., 2005a), we found three variants: rs758278442 (K31K), rs1348114695 (E35K), and rs766996587 (M82I). However, all three were either synonymous or predicted to have little impact on protein. Rs758278442 showed significant AF difference across populations, especially among east Asian populations. It is found only among east Asian individuals in gnomAD—consists of 1909 Korean, 76 Japanese, and 7212 other east Asian individuals—with AF of 0.022%. The variant is also found at Korean Reference Genome Database (*N* = 1722) with AF of 0.029%, similar value to gnomAD. However, it was found with higher AF of 0.23% at Japanese genetic variation database (*N* = 3552). Rs1348114695 at residue 35 was found only in European and east Asian populations with very low frequencies: 0.001% and 0.014%, respectively. Lastly, rs766996587 at residue 82 was found only in African population (AF = 0.026%). Nonetheless, protein modeling predicts little

topological difference between all *ACE2* variants and wild-type *ACE* in their binding to S protein (Hussain et al., 2020). Therefore, we expect minimal genetic variance across populations critically affecting interaction between *ACE2* and SARS-CoV-2. Fig. 1A illustrates the 19 variants over known functional protein domains of *ACE2*.

The proteolysis activity of *TMPRSS2* is crucial for viral entry to host cells (Hoffmann et al., 2020). Two residues, V292 and M478, are reported to impact the catalytic activity of *TMPRSS2* (Afar et al., 2001) but we found no variants at these residues (Supplementary Table 1). Reported variants for *TMPRSS2* contain 417 nonsynonymous variants including 40 loss-of-function variants. All of loss-of-function variants were very rare (AF < 0.01%). The rest of nonsynonymous variants were also of low frequencies (AF < 0.1%) mostly. Of the only 5 nonsynonymous variants with AF > 0.1%, rs12329760 (V192M, global AF = 24.88%) predicted deleterious and its AF ranged from 15.33% (Latino) to 38.38% (East Asian). Further studies are required to test whether rs12329760 could exert functional impact on *TMPRSS2* activity. Thus, differences in *TMPRSS2* activity caused either by variants at critical loci or by loss-of-function variants are unlikely. SARS-CoV-2 uses both *TMPRSS2* and the endosomal cysteine proteases cathepsin B and L (*CTSB* and *CTSL*) for priming S protein (Hoffmann et al., 2020). UniProt entries for human *CTSB* and *CTSL* report 3 active sites. We found 3 variants in the active sites for *CTSB* (two missense variants and one synonymous variant), and one missense variant for *CTSL* (Table 1 and Fig. 1B). Although all missense variants on active sites of *CTSB/L* are predicted deleterious, they were of very low allele frequencies (AF < 0.01%). *CTSB* has 429 nonsynonymous variants including 51 loss-of-function variants (all with AF < 0.01%). *CTSL* has 211 nonsynonymous variants including 17 loss-of-function variants. Of note, one of 17 variants in *CTSL* (rs2378757, NC\_000009.11:g.90343780A > C) is a common allele (global AF of 70.32%, population AF ranges from 62.66% to 98.48%). The variant changes stop codon to serine for one *CTSL* transcript isoform (ENST00000342020.5) but falls in intron for the other transcript isoforms.

Next we checked genetic variants in TLRs that sense viral RNAs and initiate innate immune responses. There were 7 variants—4 synonymous and 3 nonsynonymous—in the 16 residues of ssRNA interacting domain of TLR7 (Table 1 and Fig. 1C). Most variants were of extremely low frequencies (AF < 0.01%) except for one synonymous variant, rs769401373 (D135D), found only in east Asian population (AF = 0.46%). *TLR7* harbors 232 nonsynonymous variants including 8 loss-of-function variants. As in *TMPRSS2*, AFs of loss-of-function variants were also very low (AF < 0.01%). The UniProt entries for TLR3 and TLR8 list 10 sites (6 for TLR3 (Bell et al., 2006; de Bouteiller et al., 2005; Sarkar et al., 2007) and 4 for TLR8 (Tanji et al., 2015)) from in vitro mutagenesis study that impact their response to viral infection (sensing of dsRNA or ssRNA, respectively). For these loci, two missense variants on *TLR3* and one missense variant with one synonymous variant on *TLR8* were found (Table 1 and Fig. 1C). All of these variants in TLRs were very rare (AF < 0.01%) across all populations.

To summarize, the critical loci for host-viral interaction and sensing viral genomic RNA are highly conserved in all populations with few very rare variants. Especially, *ACE2* and *TLR7* seem to be under strong selection pressure as reflected in their relatively lower number of loss-of-function variants than expected in large variant databases such as gnomAD (Karczewski et al., 2020): three observed variants out of 31 expected ones for *ACE2* and two observed variants out of 20.7 expected ones for *TLR7*. Moreover, nonsynonymous variants in these genes were mostly of very low frequencies which suggests the chance of gene function altered by these variants would be unlikely, compared to the incidence of COVID-19 around the globe. Other factors such as existing medical conditions and environmental risk factors could contribute the regulation of expression of these key genes in susceptible individuals; however, further studies are required to elucidate potential associations.

The majority of infected individuals experience no or mild symptoms of upper respiratory tract infection; however, for some

**Table 1**  
Genetic variants in the genes related to host-viral interaction and sensing of viral RNAs.

Genes	Residues	AA changes from mutagenesis studies	Residue loci (b37)	Reported variants within the residues			Variant allele frequencies		
				Variants	RS ID	Impact	AA Change	gnomAD <sup>[1]</sup>	
								Global	African
ACE2	S19 <sup>[7,10]</sup>		X:15618978–15,618,980	NC_000023.10:- g-15618980A > G	rs73635825	Missense	S > P	0.031%	0.332%
	A25 <sup>[11]</sup>	24–26, QAK-KAE	X:15618957–15,618,965	NC_000023.10:- g-15618960G > A	rs761614932	Synonymous	=	0.001%	
	K26 <sup>[11]</sup>			NC_000023.10:- g-15618958 T > C	rs4646116	Missense	K > R	0.388%	0.095%
				NC_000023.10:- g-15618959 T > C	rs1299103394	Missense	K > E	0.001%	
	T27 <sup>[7,9]</sup>		X:15618954–15,618,956	NC_000023.10:- g-15618956 T > C	rs781255386	Missense	T > A	0.001%	
	K31 <sup>[7,9–11]</sup>	K31D	X:15618942–15,618,944	NC_000023.10:- g-15618942C > T	rs758278442	Synonymous	=	0.002%	
	H34 <sup>[7–10]</sup>		X:15618933–15,618,935	NC_000023.10:- g-15618933G > A	rs368655410	Synonymous	=	0.063%	
	E35 <sup>[7,9,10]</sup>		X:15618930–15,618,932	NC_000023.10:- g-15618932C > T	rs1348114695	Missense	E > K	0.002%	
	E37 <sup>[7,9,10]</sup>		X:15618924–15,618,926	NC_000023.10:- g-15618924C > T	rs146676783	Missense	E > K	0.004%	0.011%
	K68 <sup>[11]</sup>	K68D	X:15613109–15,613,111	NC_000023.10:- g-15613111 T > C	rs755691167	Missense	K > E	0.001%	
TLR7 <sup>[12]</sup>	M82 <sup>[7–11]</sup>	82–84, MYP-NFS	X:15613061–15,613,069	NC_000023.10:- g-15613067C > T	rs76696587	Missense	M > I	0.002%	0.026%
	P84 <sup>[11]</sup>			NC_000023.10:- g-15613063G > T	rs759134032	Missense	P > T	0.001%	
	E329 <sup>[7]</sup>		X:15599427–15,599,429	NC_000023.10:- g-15599428 T > C	rs143936283	Missense	E > G	0.003%	
	D355A		X:15599349–15,599,351	NC_000023.10:- g-15599351C > T	rs961360700	Missense	D > N	0.001%	
	P389A		X:15596342–15,596,344	NC_000023.10:- g-15596343G > T	rs762890235	Missense	P > H	0.004%	
	P426 <sup>[11]</sup>	425–427, SPD-PSN	X:15596228–15,596,236	NC_000023.10:- g-15596233G > C	rs1238146879	Missense	P > A	0.001%	
				NC_000023.10:- g-15596231G > A	rs1335386721	Synonymous	=	0.001%	
	D427 <sup>[11]</sup>			NC_000023.10:- g-15596230C > A	rs1316056737	Missense	D > Y	0.001%	0.015%
	R559 <sup>[11]</sup>		X:15589907–15,589,909	NC_000023.10:- g-15589907C > G	rs1016777825	Missense	R > S	0.001%	
	F351		X:12904678–12,904,680	NC_000023.10:- g-12904680 T > C	rs200549906	Synonymous	=	0.002%	
TLR7 <sup>[12]</sup>	L557		X:12905296–12,905,298	NC_000023.10:- g-12905296C > T	rs1419393304	Missense	L > F	0.002%	
	T586A		X:12905385–12,905,385	NC_000023.10:- g-12905385 T > A	rs185622718	Synonymous	=	0.001%	
	L105A		X:12903940–12,903,942	NC_000023.10:- g-12903940C > T	rs773554481	Synonymous	=	0.001%	
	D135A		X:12904030–12,904,032	NC_000023.10:- g-12904032 T > C	rs769401373	Synonymous	=	0.033%	
	R186A		X:12904183–12,904,185	NC_000023.10:- g-12904184G > A	rs868177091	Missense	R > Q	0.001%	

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Table 1 (continued)

Genes	Residues	AA changes from mutagenesis studies	Residue loci (b37)	Reported variants within the residues		Variant allele frequencies		
				Variants	RS ID	Impact	AA Change	gnomAD <sup>[1]</sup>
							Global	African
CTSB (CatB) <sup>[13]</sup>	R473	R473A	X:12905044–12,905,046	NC, 000023.10:- g.12905045G > A	rs754381606	Missense	R > K	0.001%
	C108		8:11708378–11,708,380	NC, 000008.10:- g.11708378G > A	rs759843078	Synonymous	=	0.002%
	H278		8:11703258–11,703,260	NC, 000008.10:- g.11703259 T > C	rs1373655221	Missense	H > R	0.0004%
								Only found in Finnish population (0.005%)
CTSL (CatL) <sup>[14]</sup>				NC, 000008.10:- g.11703260G > A	rs1225109229	Missense	H > Y	0.0004%
	C138		9:90343515–90,343,517	NC, 000009.11:- g.90343515 T > C	rs757571238	Missense	C > R	0.001%
	H539	H539E	4:187004455–187,004,457	NC, 000004.11:- g.187004456A > G	rs776387492	Missense	H > R	0.001%
TLR3 <sup>[15]</sup>	Y759	Y759F	4:187005115–187,005,117	NC, 000004.11:- g.187005115 T > C	rs768605211	Missense	Y > H	0.001%
TLR8 <sup>[16]</sup>	Y348	Y348A	X:12938201–12,938,203	NC, 000023.10:- g.12938202A > G	rs1175381548	Missense	Y > C	0.001%
				NC, 000023.10:- g.12938203 T > C	rs768875789	Synonymous	=	0.001%
								Only found in Finnish population (0.006%)

Genes	Variant allele frequencies									
	gnomAD <sup>[1]</sup>					1KGP <sup>[2]</sup>	SGDP <sup>[3]</sup>	GTEX <sup>[4]</sup>	KRGDB <sup>[5]</sup>	TogoVar <sup>[6]</sup>
	Latino	European	East Asian	South Asian						
ACE2										
	0.325%	0.587%	0.007%	0.131%	0.030%	0.333%	0.477%			
	0.007%	0.001%	0.007%		0.210%					
		0.033%	0.022%	0.026%		0.333%		0.029%	0.230%	
		0.001%	0.027%						0.040%	
			0.014%			0.333%				
				0.011%						
TLR7 <sup>[12]</sup>				0.005%						
		0.007%								
	0.018%	0.003%								
		0.002%								
		0.001%								
	0.004%	0.001%	0.007%		0.030%					
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Table 1 (continued)

Genes	Variant allele frequencies				
	gnomAD <sup>[1]</sup>				
	Latino	European	East Asian	South Asian	1KGP <sup>[2]</sup>
CTSB (CatB) <sup>[13]</sup>		0.001%	0.458%		0.050%
				0.005%	
				0.005%	
CTSL (CatL) <sup>[14]</sup> TLR3 <sup>[15]</sup>	Only found in Finnish population (0.0005%)				
	0.001%				
	0.003%				
TLR8 <sup>[16]</sup>	Only found in Finnish population (0.006%)		0.005%	0.003%	0.029%
			0.007%	0.007%	

[1] The genome aggregate database (gnomAD), v2.1.1. <https://gnomad.broadinstitute.org>. Allele frequencies for European are from Non-Finnish European population.

[2] 1000 Genomes Project (1KGP), phase 3. <https://www.internationalgenome.org>

[3] Simons Genome Diversity Project (SGDP). <https://www.simonsfoundation.org/simons-genome-diversity-project/>

[4] Gene-Tissue Expression project (GTEx), v8 whole genomes. <https://gtexportal.org/home/>

[5] Korean Reference Genome Database (KRGDB). <http://coda.nih.go.kr/coda/KRGDB/index.jsp>

[6] NBDC's integrated database of Japanese genomic variation (TogoVar). <https://togovar.biosciencedbc.jp>

[7] Shang et al., Nature, 2020

[8] Yan et al., Science, 2020

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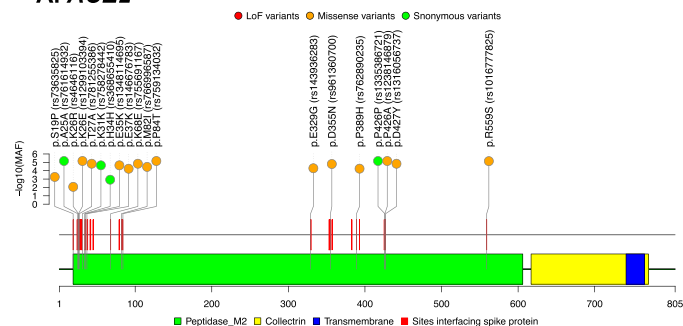
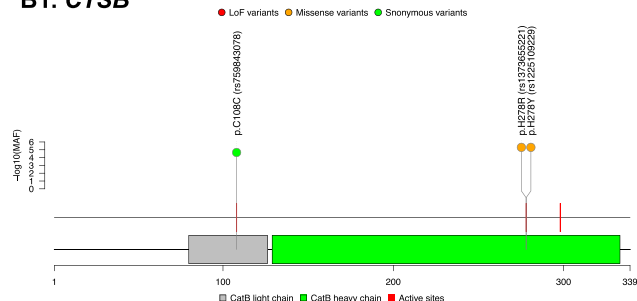
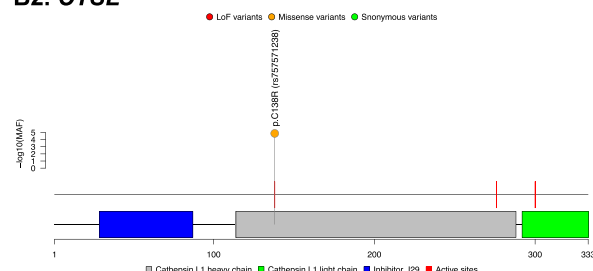
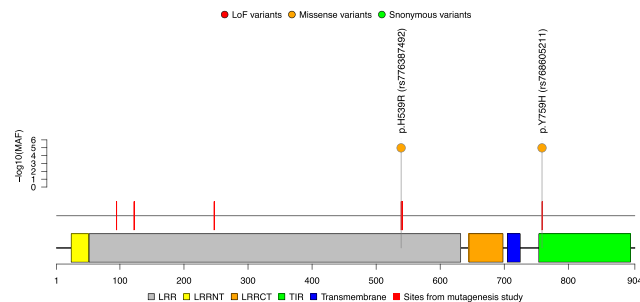
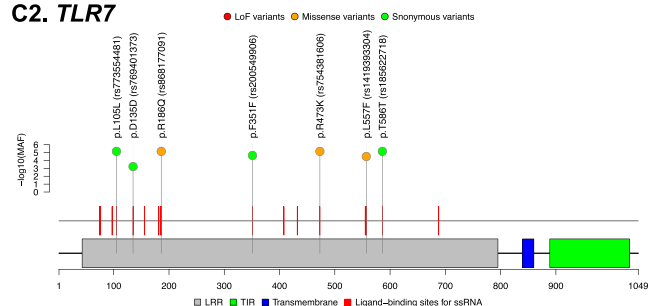
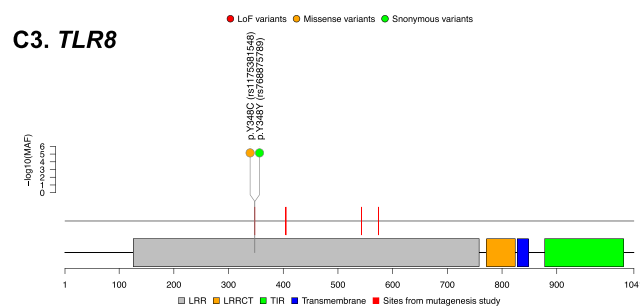
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[14] Based on active sites from UniProt protein information for P07711 (CATL1\_HUMAN). <https://www.uniprot.org/uniprot/P07711>

[15] Based on mutagenesis studies from UniProt protein information for O15455 (TLR3\_HUMAN). <https://www.uniprot.org/uniprot/O15455>

[16] Based on mutagenesis studies from UniProt protein information for Q9NR97 (TLR8\_HUMAN). <https://www.uniprot.org/uniprot/Q9NR97>

**A. ACE2****B1. CTSL****B2. CTSL****C1. TLR3****C2. TLR7****C3. TLR8**

**Fig. 1.** Location of genetic variants relative to known functional domains of (A) ACE2, (B) CTBL/L and (C) TLR3/7/8. For each gene, x-axis represents positions in protein sequence. The block diagram directly above the x-axis depicts major protein domains in different colored boxes. The vertical red lines above domains correspond to the critical residues investigated in this study. Each of the circles with grey lines represents variant found on the critical loci. The circles are colored differently based on their calculated effect on protein: loss-of-function (LoF) variants (red), missense variants (orange), and synonymous variants (green). The height of each circle denotes variant allele frequency (in  $-\log_{10}$  scale). The higher the circle, the lower the allele frequency. Of note, TMPRSS2 does not have any reported genetic variant in enzymatically active functional domain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

individuals, the consequence of SARS-CoV-2 infection could be fatal. One of the contributing factors may be the viral load due to differential affinity of viral spike proteins to ACE2 and the efficiency of cleavage by TMPRSS2 that are essential for virus to enter and replicate inside of host cells. We did not find genetic variation between populations while there is a significant difference in incidence and mortality between race and ethnic groups in the U.S. Therefore, underlying medical conditions, age, environmental factors (e.g., air pollution, smoking, and humidity), and a healthcare disparity influence morbidity and mortality from COVID-19 considering the allelic spectrum for the key genes associated with viral entry. Nonetheless, genetic susceptibility may play a role for severe cases with respiratory failure (Ellinghaus et al., 2020).

The population-scale genotype databases and datasets used in this study have limitations from relatively small sample size and imbalanced and incomplete representation of various human populations. Thus, there could be unreported variants in ACE2, TMPRSS2, and TLR3/7/8 that may be associated with change of susceptibility to COVID-19. With additional population-scale genomic databases for diverse populations, it will be possible to identify the individuals with rare genetic variants such as rs758278442 in the interacting domain of ACE2 and the genetic

predisposition to cytokine storm that causes an acute progress of illness in young people. In parallel, a systematic mutagenesis analysis of the RBM of ACE2 is highly required to understand the difference in host-viral interaction across populations (Lan et al., 2020).

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.meegid.2020.104507>.

### Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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