Genetic variants that influence SARS-CoV-2 receptor *TMPRSS2* expression among population cohorts from multiple continents

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ABSTRACT

The World Health Organization recently announced that pandemic status has been achieved for coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Exponential increases in patient numbers have been reported around the world, along with proportional increases in the number of COVID-19-related deaths. The SARS-CoV-2 infection rate in a population is expected to be influenced by social practices, availability of vaccines or prophylactics, and the prevalence of susceptibility genes in the population. Previous work revealed that cellular uptake of SARS-CoV-2 requires Angiotensin Converting Enzyme 2 (ACE-2) and a cellular protease. The spike (S) protein on SARS-CoV-2 binds ACE-2, which functions as an entry receptor. Following receptor binding, transmembrane protease serine 2 (encoded by *TMPRSS2*) primes the S protein to allow cellular uptake. Therefore, individual expression of *TMPRSS2* may be a crucial determinant of SARS-CoV-2 infection susceptibility. Here, we utilized multiple large genome databases, including the GTEx portal, SNP nexus, and Ensembl genome project, to identify gene expression profiles for *TMPRSS2* and its important expression quantitative trait loci. Our results show that four variants (rs464397, rs469390, rs2070788 and rs383510) affect expression of *TMPRSS2* in lung tissue. The allele frequency of each variant was then assessed in regional populations, including African, American, European, and three Asian cohorts (China, Japan and Taiwan). Interestingly, our data shows that *TMPRSS2*-upregulating variants are at higher frequencies in European and American populations than in the Asian populations, which implies that these populations might be relatively susceptible to SARS-CoV-2 infection.

1. Introduction

The new infectious respiratory disease, coronavirus disease 2019 (COVID-19), first emerged in Wuhan, China according to the World Health Organization (WHO) [1]. The initial cluster of infections was linked to a seafood market in Wuhan, where animal contact led to transfer of the virus to humans and then ultimately to human-to-human transmission [2]. In February of this year, the International Committee on Taxonomy of Viruses named the virus that causes COVID-19 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3] based on its close homology with SARS-CoV and its pathological sequelae that often include respiratory conditions, such as severe pneumonia [4]. The continuous increase of patients suffering from SARS-CoV-2 infection and COVID-19 across all inhabited continents (i.e., Asia, Australia, Europe, the Americas, and Africa) eventually led the WHO to declare this disease a pandemic. Strikingly, the last updated data from the coronavirus worldometer website (https://www.worldometers.info/coronavirus/) on May 07, 2020, 02:48 GMT, showed that the total

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number of confirmed COVID-19 cases in more than 210 countries was 3.822.860 while the reported deaths were 265.076. In order to slow the spread of virus and to keep the number of critical patients within the capacity of hospitals, nearly all developed nations have instituted tight restrictions on movement of their residents, which has come at an extreme economic cost. While these social policies led to a reported net decrease in the number of active cases within China in late March, the spread of disease was still rampant in other countries, highlighting the dynamic nature of the pandemic and the major challenge of suppressing spread of SARS-CoV-2 transmission simultaneously around the world.

Mitigation of disease spread would almost certainly be aided by effective vaccines or prophylactic agents that target SARS-CoV-2 cellular uptake. However, vaccines require a long development time and clinical trials for potential SARS-CoV-2 uptake inhibitors are ongoing. Recent reports have indicated that infection of lung epithelial cells with SARS-CoV-2 requires angiotensin converting enzyme 2 (ACE-2) and transmembrane protease serine 2 (encoded by *TMPRSS2*) [5]. For successful infection to occur, coronaviruses must utilize a protease from the host cell to activate the viral spike (S) protein, and *TMPRSS2* was recently reported to be an essential host factor in airway epithelial cells [6] that allows entry into the cells [5,7,8]. It is still unclear, however, whether and how *TMPRSS2* allelic variants in the lung might affect protease expression. Upregulation of *TMPRSS2*, would be expected to enhance S protein processing, and therefore, susceptibility to SARS-CoV-2 infection and COVID-19 pathogenesis. Moreover, a population with a large proportion of susceptibility gene carriers would be expected to be more vulnerable to the disease. Up to now, no susceptibility markers for COVID-19 have been identified, and no lung-associated variants in *TMPRSS2* have been reported. Here, we used various databases to assess the tissue expression profiles of *TMPRSS2* and occurrence of genetic variants in populations from several continents. The results will allow future studies assessing whether these

variants may be associated with different risks of SARS-CoV-2 infection and susceptibilities to COVID-19.

2. Methods

In order to evaluate the relationship between genetic variants and gene expression profiles, expression quantitative trait loci (eQTL) were examined using the GTEx portal database (http://www.gtexportal.org/home/), which compiles the expression of genes in a variety of tissues. The genetic variants of *TMPRSS2* in human lung tissue were obtained from the GTEx portal database and confirmed with the Ensembl Genome Browser (https://www.ensembl.org/index.html). The allele frequencies among populations of European, African, American, East Asian, Southeast Asian. Japanese, and Han Chinese were extracted from the Ensembl Genome Browser (http://www.ensembl.org/Homo_sapiens/Variation), while the allele frequency in the Taiwan population was obtained from the Taiwan Biobank website (https://taiwanview.twbiobank.org.tw/index). Annotations, such as location or type of variant, were retrieved from the Ensembl Genome Browser (https://www.ensembl.org/index.html). Variants function was evaluated using the SNP nexus database (https://www.snp-nexus.org). SNPs were prioritized based on PubMed text mining to check whether the genetic variants of interest showed any correlation in the clinical significance.

3. Results

3.1. TMPRSS2 gene expression in various tissues

In order to evaluate *TMPRSS2* expression in human tissues, we examined eQTLs using the GTEx portal database (http://www.gtexportal.org/home/), which contains gene expression levels in a variety of tissues. The eQTL annotations comprise the most
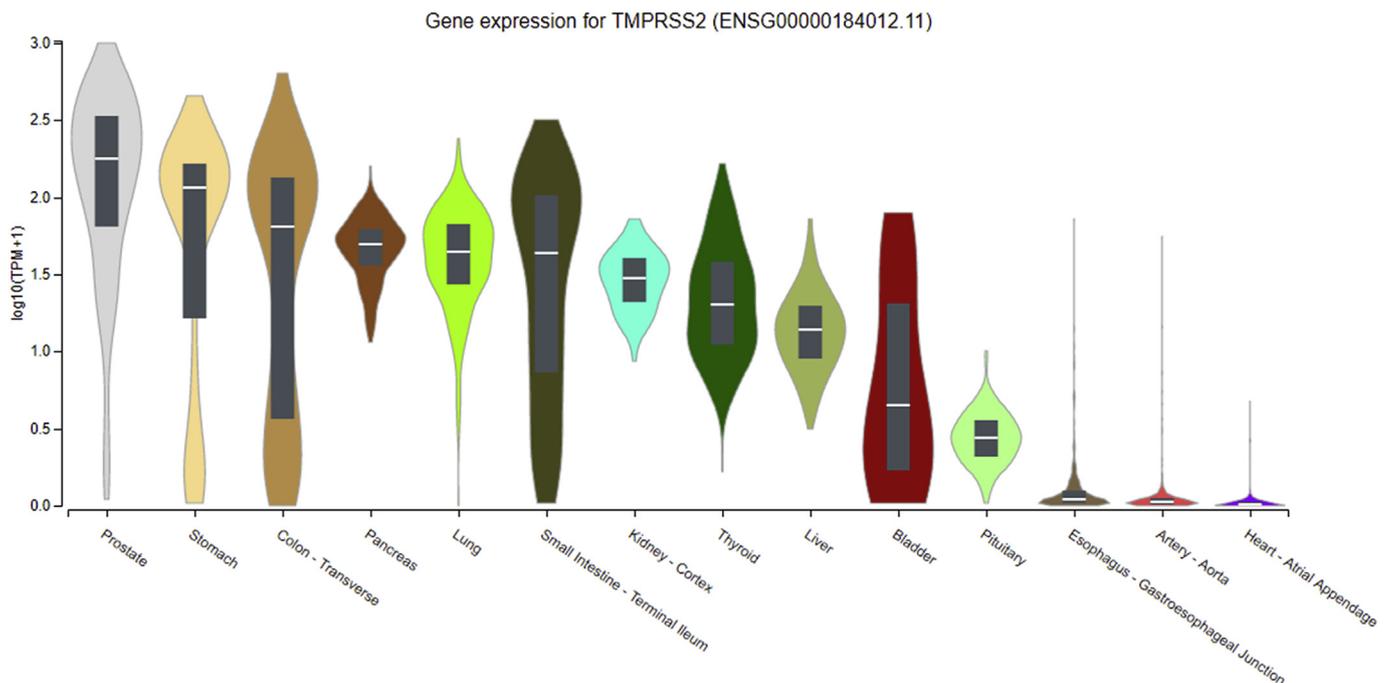
Fig. 1. Expression of transmembrane serine protease 2 (*TMPRSS2*) in different human tissues according to the GTEx database project (https://www.gtexportal.org/home).

apparent functional consequences of genetic variations [9], and the database revealed that *TMPRSS2* displays high expression in the prostate, colon, stomach, pancreas and lung (Fig. 1).

3.2. Important eQTLs for TMPRSS2 in the lung

To identify eQTLs associated with *TMPRSS2* expression in lung, the GTEx portal database was utilized. We identified a total of 203 eQTLs for *TMPRSS2* in all tissues. Among them, 136 variants indicated predominant effects on *TMPRSS2* expression in lung, while 56 eQTLs were relevant to testis, nine to prostate, one to ovary, and one to thyroid (**Additional File S1**). Next, we further examined the 136 eQTLs in lung using the SNP nexus database and PubMed text mining to determine whether the genetic variants might have the clinical significance. Among the 136 lung-associated variants, rs469390 was confirmed as a missense mutation, and three others, rs2070788, rs383510 and rs464397, were previously reported to have clinical significance in infectious disease. Cheng at al., revealed that two genetic variants rs2070788 and rs383510 were significantly associated with the susceptibility to influenza [10], while rs464397 was reported to associate with poor immune response in patients co-infected with HIV and HCV [11]. Therefore, our

subsequent analyses were focused on these four SNPs. Three of them (rs2070788, rs383510 and rs464397) are located at the intronic region and one (rs469390) is located at the exon region, as depicted in Fig. 2.

3.3. Association between TMPRSS2 expression and the four eQTLs

We next tested potential associations between the four identified variants (rs464397, rs469390, rs2070788 and rs383510) and *TMPRSS2* expression in lung. Using the publicly available GTEx Portal (http://www.gtexportal.org/home/), we obtained the tissue expression of *TMPRSS2* across different genotypes in each eQTL from 515 samples. As shown in Table 1 and Fig. 3, the TT genotype of rs464397 was associated with higher expression of *TMPRSS2* and *MX1* in the lung compared to the CT and CC genotypes. Furthermore, the AA genotype of rs469390 was associated with higher expression of *TMPRSS2* and *MX1* in the lung compared to the AG and GG genotypes, and the rs2070788 GG genotype had higher expression of *TMPRSS2* and *MX1* in the lung compared to the AG and AA genotypes. Lastly, the rs383510 TT genotype was associated with higher expression of *TMPRSS2* in the lung compared to the CT and CC genotypes.
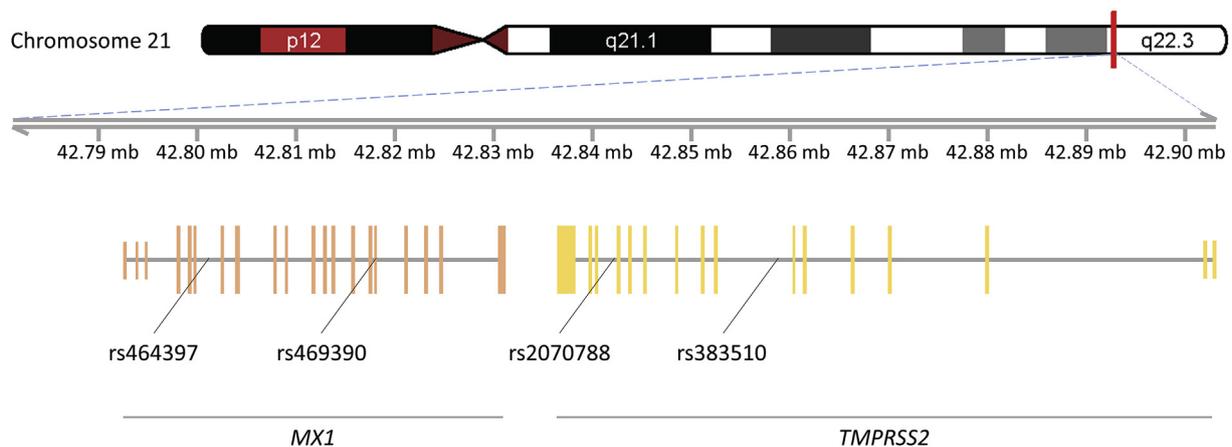
Fig. 2. The location of selected variants (rs469390, rs2070788, rs383510 and rs464397) on chromosome 21.

Table 1
Cis-expression of quantitative trait loci results for the transmembrane serine protease 2 (*TMPRSS2*) SNPs from genotype-tissue expression database.

SNP ID	Gencode ID (ENSG00000-)	Gene symbol	*p*-value	Effect size	Tissue	Actions
rs464397	184012.11	*TMPRSS2*	0.000010	−0.08	**Lung**	TT > TC > CC
	157601.13	*MX1*	2.1e-13	−0.31	Thyroid	TT > TC > CC
rs469390	184012.11	*TMPRSS2*	0.0000068	0.091	**Lung**	AA > AG > GG
	157601.13	*MX1*	1.40E-13	0.32	Thyroid	AA > AG > GG
	157601.13	*MX1*	4.50E-12	0.27	Nerve - Tibial	AA > AG > GG
	157601.13	*MX1*	9.00E-08	0.25	**Lung**	AA > AG > GG
	157601.13	*MX1*	5.60E-07	0.2	Artery - Tibial	AA > AG > GG
	157601.13	*MX1*	8.60E-07	0.21	Breast - Mammary Tissue	AA > AG > GG
	157601.13	*MX1*	1.1E-06	0.18	Muscle - Skeletal	AA > AG > GG
	157601.13	*MX1*	1.5E-06	0.2	Skin - Not Sun Exposed (Suprapubic)	AA > AG > GG
	157601.13	*MX1*	3.3E-06	0.18	Esophagus - Mucosa	AA > AG > GG
	157601.13	*MX1*	3.8E-06	0.19	Esophagus - Muscularis	AA > AG > GG
	157601.13	*MX1*	4.8E-06	0.21	Testis	AA > AG > GG
	157601.13	*MX1*	0.000013	0.22	Colon - Transverse	AA > AG > GG
	157601.13	*MX1*	0.000014	0.24	Esophagus - Gastroesophageal Junction	AA > AG > GG
	157601.13	*MX1*	0.000023	0.16	Skin - Sun Exposed (Lower leg)	AA > AG > GG
	157601.13	*MX1*	0.000043	0.21	Artery - Aorta	AA > AG > GG
rs2070788	184012.11	*TMPRSS2*	8.9e-9	−0.11	**Lung**	GG > AG > AA
	157601.13	*MX1*	0.000012	−0.18	Thyroid	GG > AG > AA
rs383510	184012.11	*TMPRSS2*	1.2e-8	−0.11	**Lung**	TT > TC > CC

Source: Expression Quantitative trail loci (eQTL) obtained from https://gtexportal.org/home.

3.4. Allele frequencies of the candidate variants in different populations

Once we had identified the four candidate *TMPRSS2* expression-associated variants, we were interested to know the allele frequencies in different populations. As shown in Table 2, the allele frequencies for the four variants were evaluated in different populations from Europe, Africa, America, East Asia, Southeast Asia, Japan, China (Han) and Taiwan. Samples from each region contains 503 individuals (European), 661 individuals (African), 347 individuals (American), 504 individuals (East Asian), 489 individuals (Southeast Asian). Among the East Asians, the subpopulations include103 Han Chinese and 104 Japanese. Furthermore, allele frequencies in a group of 1517 individuals from Taiwan Biobank

were also assessed. Allele frequencies in European, African, American, East Asian, and Southeast Asian populations were extracted from the Ensembl Genome Browser (http://www.ensembl.org/Homo_sapiens/Variation). The Taiwan Biobank was queried using the Taiwan View website (https://taiwanview.twbiobank.org.tw/index) to examine the Taiwanese population. The allele frequencies across different populations for each *TMPRSS2*-upregulating variants are shown in Table 2 and Fig. 4. Strikingly, the frequency of rs464397 T allele, which is associated with higher *TMPRSS2* expression in lung, is much lower in the Asian (East Asian and Southeast Asian) populations compared to European, African and American populations. Cohorts from China, Japan and Taiwan exhibited the lowest T allele frequencies of rs464397 (~1%). In addition, the frequencies of rs383510 T allele and rs469390 A allele,
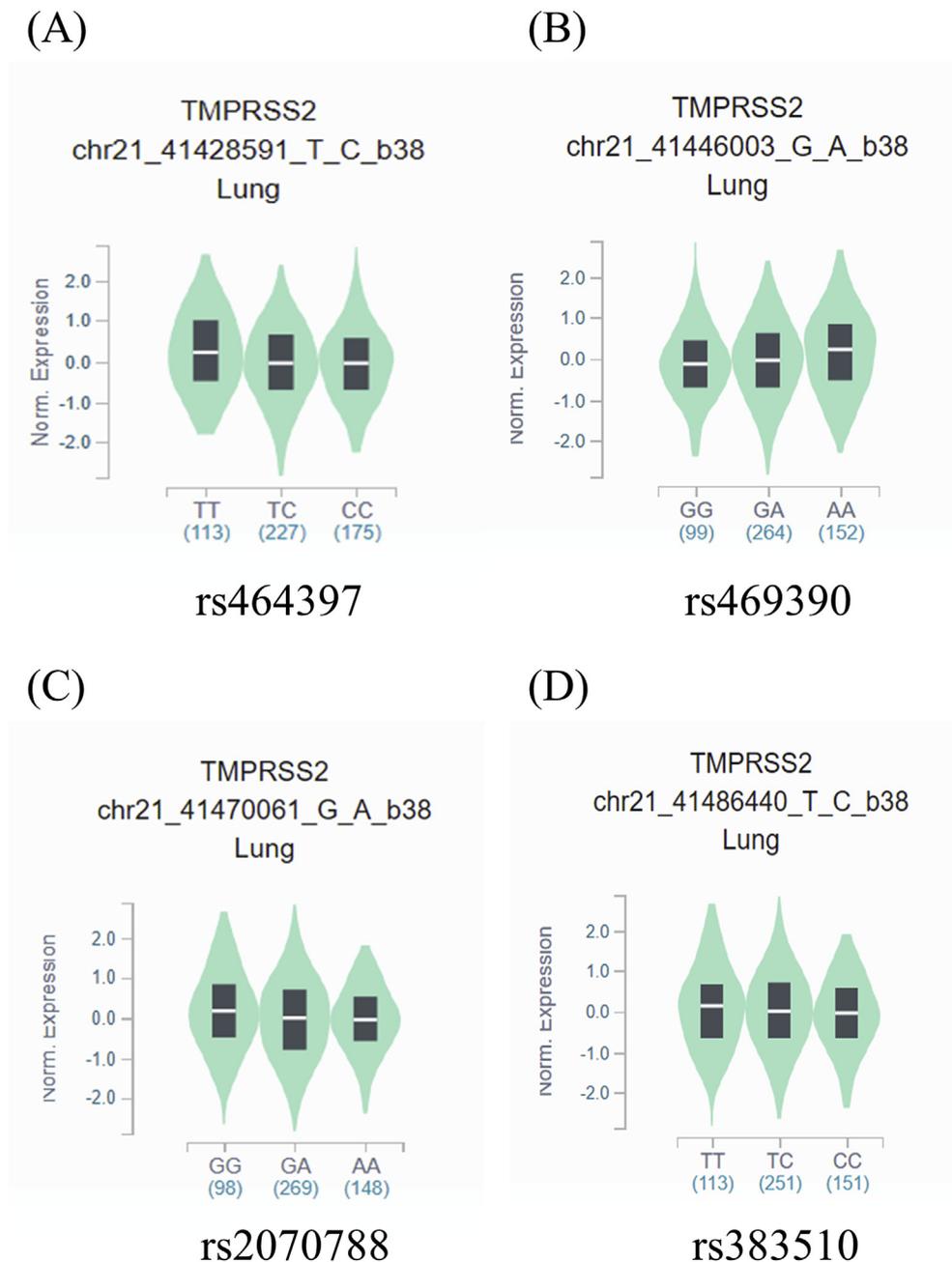
Fig. 3. *Cis*-expression of quantitative trait loci results for transmembrane serine protease 2 (*TMPRSS2*) in lung tissue. Plots show the expression of *TMPRSS2* for each genotype of the four SNPs: rs464397 (A), rs469390 (B), rs2070788 (C) and rs383510 (D).

Table 2
Allele frequencies for transmembrane serine protease 2 (*TMPRSS2)* SNPs examined in this study.

SNP	Position (hg19) (bp)	Gene	Location	Amino Acid Change	Allele		Allele Frequencies(N)							
					Ref	Eff*	EUR (503)	AFR (661)	AMR (347)	EAS (504)	SAS (489)	CHB (103)	JPT (104)	TWB (1517)
rs464397	Chr 21:42800518	*MX1*	Intron	–	C	T	0.48	0.14	0.32	0.01	0.25	0.01	0.01	0.01
rs469390	Chr 21:42817930	*MX1*	Exon	Val/Ile	G	A	0.59	0.44	0.45	0.28	0.55	0.21	0.20	0.26
rs2070788	Chr 21:42841988	*TMPRSS2*	Intron	–	A	G	0.46	0.27	0.49	0.36	0.47	0.28	0.30	0.34
rs383510	Chr 21:42858367	*TMPRSS2*	Intron	–	C	T	0.48	0.33	0.38	0.36	0.46	0.27	0.30	0.34

EUR, European; AFR, African; AMR, American; EAS, East Asian; SAS, Southeast Asian. JPT, Japanese in Tokyo, CHB, Han Chinese and TWB, Taiwan Biobank. N; total number of samples, Ref, Reference and Eff, Effect allele of EUR, AFR, AMR, EAS, SAS, CHB, JPT were extracted from the Ensembl.org (http://www.ensembl.org/Homo_sapiens/Variation). TWB were obtained from the Taiwan View website (http://taiwanview.twbiobank.org.tw/index). * Effect allele is defined as the allele associated with higher expression *TMPRSS2* in lung.

which are also associated with higher *TMPRSS2* expression in lung, are lower in East Asian populations compared to European and American populations (Fig. 4). The respective G and A allele frequencies for rs2070788 and rs383510 also appeared to have lower prevalence in East Asia (rs2070788, 36% and rs383510, 36%), China (rs2070788, 28% and rs383510, 27%), Japan (rs2070788, 30% and rs383510, 30%) and Taiwan (rs2070788, 34% and rs383510, 34%) compared to the European population (rs2070788, 46% and rs383510, 48%) and American (rs2070788, 49% and rs383510, 38%) (Table 2). Taken together, the allele frequencies of variants rs464397, rs469390, rs2070788 and rs383510 would suggest that expression of *TMPRSS2* may be lower in East Asian populations compared to European and American populations.

4. Discussion

In this work, we examined the lung tissue expression of the *TMPRSS2* gene, as ACE2 and *TMPRSS2* encode necessary components for cell entry of SARS-CoV [12] and SARS-CoV-2 [13]. Coronavirus infection requires a host cell protease to activate the viral S protein and allow entry into airway epithelial cells. One such

protease-encoding gene, *TMPRSS2*, was recently reported to be a host factor essential for viral uptake [6]. Furthermore, the gene product of *TMPRSS2* is known to activate coronavirus S proteins and allow entry of SARS-CoV and MERS-CoV [5,14]. In vitro and in vivo studies of *TMPRSS2* revealed its role in viral replication and pathogenicity of influenza A(H7N9), and A(H1N1) pdm09 [15,16] as well. However, the variants that associate to *TMPRSS2* expression have not been reported. Since COVID-19 has already had serious impacts on the world, examining the distribution of *TMPRSS2* variants may be an important pursuit, which allows us to understand infection susceptibilities in different populations. While the demographic characteristics associated with individual susceptibility to SARS-CoV-2 remain unknown, it will be interesting to study how variants in the protease and in ACE2 [17] affect viral transmission.

We utilized publicly available databases, such as GTEx portal, SNP nexus, and Ensembl to examine the genetic variants associated with *TMPRSS2* expression in lung tissue, the major site of infection for SARS-CoV-2 [4,18,19]. Notably, the *TMPRSS2* acts as a host protease in the human respiratory tract and gastrointestinal tract [20], which can explain many of the symptoms of COVID-19, such as cough, sore throat, rhinorrhea, and shortness of breath [21,22].
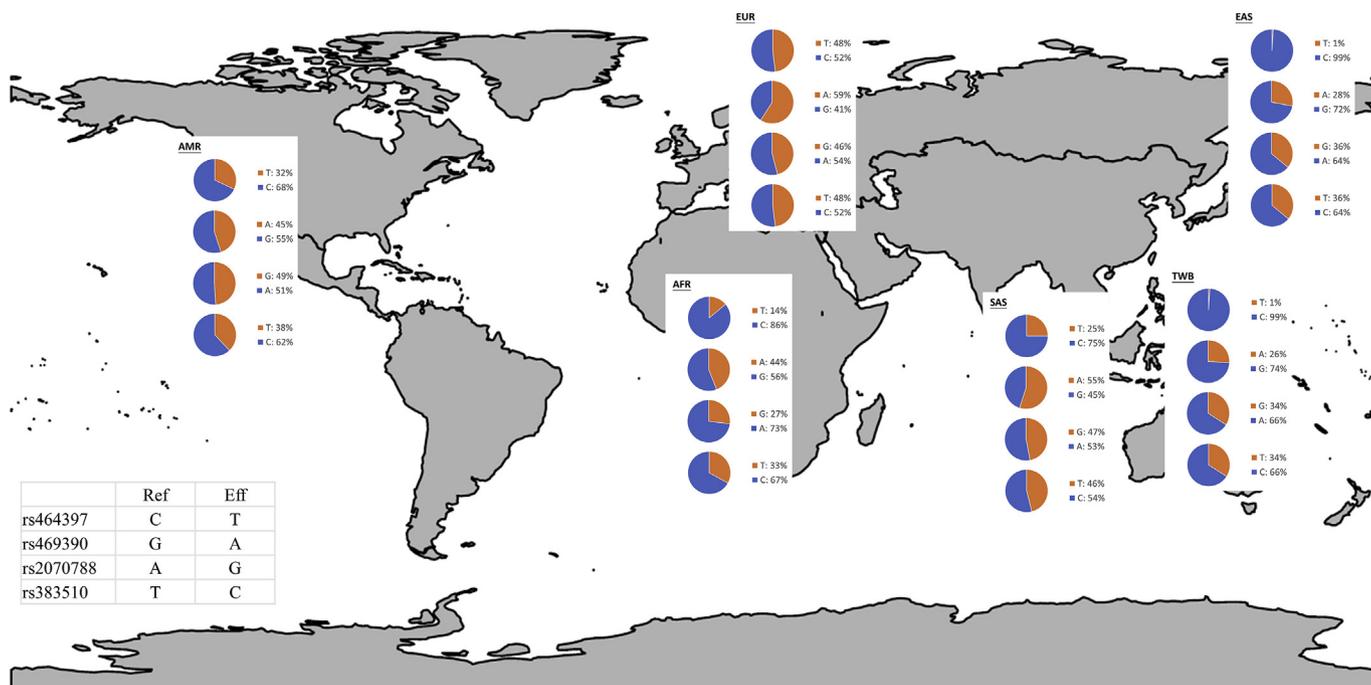
Fig. 4. The distribution of allele frequencies that influences *TMPRSS2* expression among different populations. Pie charts show the distributions of four variants (rs464397, rs469390, rs2070788 and rs383510) in various populations. EUR, European; AFR, African; AMR, American; EAS, East Asian; SAS, Southeast Asian and TWB, Taiwan Biobank. The alleles associated with higher expression of *TMPRSS2* in lung tissue are shown in orange in the pie charts. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Moreover, high SARS-CoV-2 viral loads were identified in respiratory tract specimens obtained from 18 patients in Zhuhai, Guangdong, China [23], further suggesting that respiratory tract tissue is a major target for the new virus. In the present study, we found *TMPRSS2* is highly expressed in the lung. The expression of *TMPRSS2* might be expected to influence the severity of phenotype, and in support of this idea, Yoshikawa et al. found that a lack of *TMPRSS2* in the airways reduces the severity of lung pathology after infection by SARS-CoV and MERS-CoV [14].

In this study, we found that rs469390, rs2070788, rs383510 and rs464397 are associated with differential expression of *TMPRSS2*. Furthermore, rs469390 encodes a missense mutation and the AA genotype had highest expression of *TMPRSS2* in lung, with heterozygous AG carriers showing intermediate expression and the homozygous GG genotype with lowest expression (Fig. 3). According to this finding, rs469390 has potential to be associated with susceptibility to COVID-19. We suspect that the high expression AA genotype of rs469390 may be associated with higher susceptibility to the disease. Furthermore, the A allele was present at a low frequency in Asian populations, as compared to the European and American populations (Fig. 4). In addition, the rs464397 and rs383510 homozygous TT genotypes had the highest expression in lung, compared to the heterozygous CT (intermediate expression) and homozygous CC genotype (lowest expression). The T alleles of rs464397 and rs383510 exhibited lower frequency in East Asian populations compared to European and American populations, suggesting that a relatively high percentage of Europeans and Americans may have upregulated *TMPRSS2* expression associated with these genotypes. We also found the rs2070788 with GG genotype had the highest expression in lung compared to heterozygous AG and AA genotypes. This finding was consistent with a previous study that showed rs2070788 carriers with GG genotype have higher risk for severe A (H1N1) pdm09 influenza and avian human A (H7N9) influenza [10]. The G allele frequency for rs2070788 appeared to be lower in Asian populations compared to the European and American populations as well. Overall, the frequencies of variant alleles (rs464397, rs469390, rs2070788 and rs383510) associated with high *TMPRSS2* expression in lung seemed to be lower in East Asian populations compared to European, African and American populations. Thus, the European, African and American populations may have more individuals with elevated *TMPRSS2* expression, which might lead to higher susceptibility to COVID-19.

5. Conclusion

Our identification of four genetic variants with higher *TMPRSS2* expression in lung has implications for SARS-CoV-2 susceptibility in individuals and populations. We found that rs464397, rs469390, rs2070788 and rs383510 all have effects on expression of *TMPRSS2* and occur at different frequencies in various populations. Thus, the allele frequency of each variant may be an important consideration when predicting the susceptibility of populations to coronaviruses. Based on these results, future studies may examine these four variants in COVID-19 patients and assess whether any are associated with disease susceptibility and severity.

Contributions

LMI, WHC and WCC conceived and designed the study and performed all data analyses. LMI, WHC, WA, MJC, WCC and SLH interpreted the results. LMI, WHC, MJC and WCC wrote the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors disclose no conflict.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrc.2020.05.179.

Abbreviations

ACE-2	Angiotensin Converting Enzyme 2
COVID-19	Corona virus disease 2019
CADD	Combined Annotation Dependent Depletion
e-QTL	Expression quantitative trait loci
ICTV	International Committee on Taxonomy of Viruses
WHO	World Health Organization
MERS	Middle East respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TMPRSS2	Transmembrane protease serine *2*

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