Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Genetic variants that influence SARS-CoV-2 receptor TMPRSS2 expression among population cohorts from multiple continents

Lalu Muhammad Irham, Wan-Hsuan Chou, Marcus J. Calkins, Wirawan Adikusuma, Shie-Liang Hsieh, Wei-Chiao Chang

ARTICLE INFO

Article history:
Received 25 May 2020
Accepted 25 May 2020
Available online 8 June 2020

Keywords:
SARS-CoV-2
COVID-19
TMPRSS2
Variant gene

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...
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
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 intrinsic 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.](https://gtexportal.org/home/)

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

| SNP   | GenoCode ID (ENSG0000000-) | Gene symbol | p-value | Effect size | Tissue                             | Actions |
|-------|---------------------------|-------------|---------|-------------|------------------------------------|---------|
| rs46397 | 184012.11 | TMPRSS2 | 0.0000010 | -0.08 | Lung         | TT > TC > CC |
| rs469390 | 157601.13 | MX1     | 2.1e-13 | -0.31 | Thyroid      | TT > TC > CC |
| rs2070788 | 184012.11 | TMPRSS2 | 0.0000068 | 0.091 | Lung         | AA > AG > GG |
| rs383510 | 157601.13 | MX1     | 4.50e-12 | 0.27 | Nerve - Tibial | AA > AG > GG |
| rs464397 | 157601.13 | MX1     | 9.00e-08 | 0.25 | Lung         | AA > AG > GG |
| rs2070788 | 157601.13 | MX1     | 6.00e-07 | 0.21 | Breast - Mammary Tissue | AA > AG > GG |
| rs383510 | 157601.13 | MX1     | 1.1e-06 | 0.18 | Muscle - Skeletal | AA > AG > GG |
| rs464397 | 157601.13 | MX1     | 1.5e-06 | 0.18 | Skin - Not Sun Exposed (Suprapubic) | AA > AG > GG |
| rs2070788 | 157601.13 | MX1     | 3.8e-06 | 0.19 | Esophagus - Muscosa | AA > AG > GG |
| rs383510 | 157601.13 | MX1     | 4.8e-06 | 0.21 | Esophagus - Muscularis | AA > AG > GG |
| rs2070788 | 157601.13 | MX1     | 0.000014 | 0.24 | Testis       | AA > AG > AA |
| rs383510 | 157601.13 | MX1     | 0.000023 | 0.16 | Colon - Transverse | AA > AG > AA |
| rs464397 | 157601.13 | MX1     | 0.000043 | 0.21 | Esophagus - Gastrosophageal Junction | AA > AG > AA |
| rs2070788 | 157601.13 | MX1     | 8.9e-10 | 0.11 | Skin - Sun Exposed (Lower leg) | AA > AG > AA |
| rs383510 | 157601.13 | MX1     | 1.2e-12 | 0.11 | Lung         | TT > TC > CC |

Source: Expression Quantitative trait 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 include 103 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).](image-url)
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](image_url)
Moreover, high SARS-CoV-2 viral loads were identified in respiratory tract specimens obtained from 18 patients in Zuhuai, 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 have all 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

This work was supported by the grants from Ministry of Science and Technology, Taiwan (105-2628-B-038-001-MY4; 108-2314-B-038-027) and Taipei Medical University (106-5807-001-400; Yusuke Nakamura Chair Professorship, 2020). Part of the data were extracted from the Genotype-Tissue Expression (GTEx) Portal on 03/20/2020.

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 Coronavirus 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

References

[1] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, C. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506.
[2] J.F. Chan, S. Yuan, K.H. Kok, K.K. To, H. Chu, J. Yang, F. Xing, J. Liu, C.Y. Pip, R.W. Poong, H.W. Tsos, S.K. Lo, K.H. Chan, V.K. Poong, W.M. Chan, J.D. Ip, J.P. Cai, V.C. Cheng, H. Chen, C.K. Hui, K.Y. Yuen, A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster, Lancet 395 (2020) 514–523.
[3] W.H. Organization, Naming the Coronavirus Disease (COVID-19) and the Virus that Causes it, 2020.
[4] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, W. Tan, A Novel Coronavirus from Patients with Pneumonia in China, 2019, 382, 2020, pp. 727–733.
[5] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Kruger, S. Erichsen, T.S. Schiergens, G. Gersch, H.N. Wu, A. Nitsche, M.A. Muller, C. Drosten, S. Pohlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280, https://doi.org/10.1016/j.cell.2020.02.052.
[6] M. Laporte, L. Naens, Airway proteases: an emerging drug target for influenza and other respiratory virus infections, Curr. Opin. Virol. 24 (2017) 16–24.
[7] W.-L. Wu, M.J. Moore, N. Vasilieva, J. Sui, S.K. Wong, M.A. Berne, M. Somasundaran, J.L. Sullivan, K. Luzuriaga, T.C. Greenough, H. Choe, M. Farzan, Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus, Nature 426 (2003) 450–454.
[8] I. Glowacka, S. Bertram, M.A. Muller, P. Allen, E. Soilleux, S. Pfefferle, I. Steffen, T.S. Tsegaye, Y. He, K. Gnirss, D. Schneider, M. Farzan, Genetics of gene control by the humoral immune response, J. Virol. 85 (2011) 4122–4134.
[9] V. Emilsson, G. Thorleifsson, B. Zhang, A.S. Leonardson, F. Zink, J. Zhu, S. Carlson, A. Helgason, G.B. Walters, S. Gunnarsdottir, M. Mouy, V.R. Steinhosdottir, G.H. Eiriksdottir, G. Bjornsdottir, L. Reynisdottir, D. Gudbjartsson, A. Helgadottir, A. Jonasdottir, A. Jonasdottir, U. Styrkarsdottir, S. Gretarsdottir, K.P. Magnusson, H. Stefansson, R. Fossdal, K. Kristjansson, H.G. Gislason, T. Stefansson, B.G. Leifsson, U. Thorsteinsdottir, J.R. Lamb, J.R. Culcher, M.L. Reitman, A. Kong, E.E. Schadt, K. Stefansson, Genetics of gene expression and its effect on disease, Nature 452 (2008) 423–428.
[10] Z. Cheng, J. Zhou, K.K. To, H. Chu, C. Li, D. Wang, D. Yang, S. Zheng, K. Hao, Y. Bosse, M. Obediat, C.A. Brandsma, Y.Q. Song, Y. Chen, B.J. Zheng, L. Li, K.Y. Yuen, Identification of TMPRSS2 as a susceptibility gene for severe 2009
pandemic A(H1N1) influenza and A(H7N9) influenza, J. Infect. Dis. 212 (2015) 1214–1221.

[11] M. García-Alvarez, J. Berenguer, M.A. Jiménez-Sousa, D. Pineda-Tenor, T. Aldáz-Carvajal, F. Tejerina, C. Diez, S. Vázquez-Morón, S. Resino, Mx1, OAS1 and OAS2 polymorphisms are associated with the severity of liver disease in HIV/HCV-coinfected patients: a cross-sectional study, Sci. Rep. 7 (2017) 41516.

[12] L. Glowacka, S. Bertram, M.A. Müller, P. Allen, E. Soilleux, S. Pfefferle, I. Steffen, T.S. Tsegaye, Y. He, K. Gnirss, D. Niemeyer, H. Schneider, C. Drosten, S. Pohlmann, Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response, J. Virol. 85 (2011) 4122–4134.

[13] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.H. Wu, A. Nitsche, M.A. Müller, C. Drosten, S. Pohlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, J. Virol. 88 (2014) 5608–5616.

[14] K. Sakai, Y. Ami, M. Tahara, T. Kubota, M. Anraku, M. Abe, N. Nakajima, T. Sekizuka, K. Shirato, Y. Suzuki, A. Aina, Y. Nakatsu, K. Kanou, K. Nakamura, T. Suzuki, K. Komase, E. Nobusawa, K. Maenaka, M. Kuroda, H. Hasegawa, Y. Kawaoaka, M. Tashiro, M. Takeda, The host protease TMPRSS2 plays a major role in vivo replication of emerging H7N9 and seasonal influenza viruses, J. Virol. 88 (2014) 5608–5616.

[17] Y. Zhao, Z. Zhao, Y. Wang, Y. Zhou, Y. Ma, W. Zuo, Single-cell RNA Expression Profiling of ACE2, the Putative Receptor of Wuhan 2019-nCoV, 2020, 2020.01.20.20019985.

[18] J. Gu, E. Gong, B. Zhang, J. Zheng, Z. Gao, Y. Zhong, W. Zou, J. Zhan, S. Wang, Z. Xie, H. Zhuang, B. Wu, H. Zhong, H. Shao, W. Fang, D. Gao, F. Pei, X. Li, Z. He, D. Xu, X. Shi, V.M. Anderson, A.S. Leong, Multiple organ infection and the pathogenesis of SARS, J. Exp. Med. 202 (2005) 415–424.

[19] S. Matsuyama, N. Nao, K. Shirato, M. Kawase, S. Saito, I. Takayama, N. Nagata, T. Sekizuka, H. Katoh, F. Kato, M. Sakata, M. Tahara, S. Kutsuna, N. Ohnagari, M. Kuroda, T. Suzuki, T. Kageyama, M. Takeda, Enhanced isolation of SARS-CoV-2 by TMPRSS2-Expressing Cells, 2020, 202002589.

[20] I. Ghinai, T.D. McPherson, J.C. Hunter, H.L. Kirking, D. Christiansen, K. Joshi, R. Rubin, S. Morales-Estrada, S.R. Black, M. Pacilli, M.J. Fricchione, R.K. Chugh, K.A. Wallblay, N.S. Ahmed, W.C. Stoecker, N.F. Hasan, D.P. Burdsall, H.E. Reese, M. Wallace, C. Wang, D. Moeller, J. Korpics, S.A. Novosad, L. Benowitz, M.W. Jacobs, V.S. Daari, M.T. Patel, J. Kauerauf, E.M. Charles, N.O. Ezike, V. Chu, C.M. Midgley, M.A. Rolles, S.I. Gerber, X. Lu, S. Lindstrom, J.R. Verani, J.E. Layden, First Known Person-To-Person Transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in the USA, Lancet, London, England., 2020.