



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.



Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en



Letter to the editor

Sex-mediated effects of ACE2 and TMPRSS2 on the incidence and severity of COVID-19; The need for genetic implementation



Keywords:
 COVID-19
 ACE2
 TMPRSS2

TO THE EDITOR:

Inter-individual variability regarding incidence, severity and mortality rate of Corona Virus disease 2019 (COVID-19) outbreak, was recently recorded. Thus, a different approach of infection analysis is required. Human genetics, where different genetic polymorphisms of specific genes, might account for higher susceptibility and unexpected outcomes of COVID-19 infections in different population. Recently, it was found that both Angiotensin Converting Enzyme 2 (ACE2) and Trans-membrane protease serine type 2 (TMPRSS2), are playing a crucial role for virus entry into host cells, where, ACE2 is considered the main receptor for (S) protein spike, through which the virus can attach to the target cells. While TMPRSS2 cleaves the (S) protein, allowing further fusion of virus and cellular membrane. Between supporters and opponents to the association of ACE and TMPRSS2 genetic polymorphisms to COVID-19, we will, briefly, overview and present the available scientific knowledge, about their role in the pathogenesis of COVID-19, up to the current day.

Angiotensin Converting Enzyme can show contradictory roles in the context of COVID-19, as the reduced activity of ACE2 has been reported to be associated with acute respiratory distress syndrome (ARDS). On the other hand, the increase in ACE2 expression was related to higher risk of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) activity, and development on the early disease phase [1].

Angiotensin converting enzyme genetic polymorphisms

Angiotensin Converting Enzyme (ACE) can show numerous genetic variations, such as Insertion/Deletion (Ins/Del) functional polymorphism, with the deletion allele (Del) believed to show higher ACE activity, and reduced ACE2 expression [2]. While **Delanghe** et al., has found negative correlation between ACE Del allele frequency and prevalence/mortality of COVID-19 in 33 countries, [3], **Sadaat** et al., has argued against the association between the Del allele and COVID-19 [4]. Similarly, **Chiu** et al., also reported that ACE2 gene polymorphisms had failed to affect the outcome of severe acute respiratory syndrome [5].

It is worthy to mention that ACE2 gene is located on X-chromosome, which might raise the gender-related susceptibility hypothesis, leaving females to be potentially heterozygous

(with lower sensitivity against severe infection) compared to males who are definitely hemizygous [6]. This seems to be in agreement with the finding that conversion of Angiotensin II to Angiotensin (1–7) by ACE2 was higher in males, suggesting an over-expression of ACE2 in men. In accordance to this, men were reported to be presented with 66%–75% of most severe cases [7]. Moreover, **Jin** et al., has reported that men with COVID-19 are at higher risk for worse outcomes (2.4 times higher), along with higher mortality rate, independent of age [7].

TMPRSS2 genetic polymorphisms

Besides the role of TMPRSS2 in assisting (S) protein priming, it is also claimed to mediate sex-related effects. Being an androgen responsive gene, single nucleotide polymorphisms (SNPs) within the TMPRSS2 gene (21q22.3), seems to have key role in the general population (rs2070788, rs7364083, rs9974589), and in a sex-related perspective (rs8134378). This may explain the higher expression of SARS-COV-2 in males, that might favor the virus fusion to membrane. This comes in line with the previous genome wide association studies on A(H1N1) and A(H7N9) influenza virus back in 2015 [8]. On the other hand, the fall in estrogen levels in post-menopausal women in turn can then affects the TMPRSS2 gene expression, as the gene is also being responsive to estrogen signaling [9,10]. Thus, the low levels of androgens in women can suffice to sustain TMPRSS2 expression. **Lamy** et al., also suggested that the putative androgen dependence for the virus cell entry relative to the higher expression of TMPRSS2 in males, could explain the higher male mortality with COVID-19 [11]. However, the transcriptional inhibition as a therapeutic strategy for COVID-19 is now to be implemented in knock-out mouse models [12].

The actual role of ACE Del allele in the incidence and mortality of COVID-19, is still debatable, and merit further studies and investigations. Both ACE2 and TMPRSS2 over gene-expression in males, may raise the hypothesis of male predominance in COVID-19 pandemic, along with the higher severity and worse outcome. Combining both clinical research with genetic research, can indeed help us better understand and control COVID-19.

Funding acquisition

None

Declaration of Competing Interest

All authors declares no conflict of interest.

CRediT authorship contribution statement

Mona Alshahawy: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing - original draft, Writing - review

& editing. **Mohamed Raslan:** Data curation, Formal analysis. **Nagwa Sabri:** Conceptualization, Supervision, Validation, Writing - review & editing.

References

- [1] Kłhufek J. The role of angiotensin-converting enzyme 2 in the pathogenesis of COVID-19: the villain or the hero? *Acta Clin Belg* 2020;1–8.
- [2] Delanghe JR, Speeckaert MM, De Buyzere ML. The host's angiotensin-converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections. *Clin Chim Acta* 2020;505:192–3.
- [3] Delanghe JR, Speeckaert MM, De Buyzere ML. COVID-19 infections are also affected by human ACE1 D/I polymorphism. *Clin Chem Lab Med (CCLM)* 2020;1:.
- [4] Saadat M. No significant correlation between ACE Ins/Del genetic polymorphism and COVID-19 infection. *Clin Chem Lab Med (CCLM)* 2020;1:.
- [5] Chiu RW, Tang NL, Hui DS, Chung GT, Chim SS, Chan KA, et al. ACE2 gene polymorphisms do not affect outcome of severe acute respiratory syndrome. *Clin Chem* 2004;50:1683–6.
- [6] Gemmati D, Bramanti B, Serino ML, Secchiero P, Zauli G, Tisato V. COVID-19 and individual genetic susceptibility/receptivity: role of ACE1/ACE2 genes, immunity, inflammation and coagulation. Might the double X-Chromosome in females be protective against SARS-CoV-2 compared to the single X-Chromosome in males? *Int J Mol Sci* 2020;21:3474.
- [7] Jin J-M, Bai P, He W, Wu F, Liu X-F, Han D-M, et al. Gender differences in patients with COVID-19: focus on severity and mortality. *Front Public Health* 2020;8:152.
- [8] Cheng Z, Zhou J, KK-W To, Chu H, Li C, Wang D, et al. Identification of TMPRSS2 as a susceptibility gene for severe 2009 pandemic A (H1N1) influenza and A (H7N9) influenza. *J Infect Dis* 2015;212:1214–21.
- [9] Setlur SR, Mertz KD, Hoshida Y, Demichelis F, Lupien M, Perner S, et al. Estrogen-dependent signaling in a molecularly distinct subclass of aggressive prostate cancer. *J Natl Cancer Inst* 2008;100:815–25.
- [10] Lucas JM, Heinlein C, Kim T, Hernandez SA, Malik MS, True LD, et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. *Cancer Discov* 2014;4:1310–25.
- [11] Lamy P-J, Rébillard X, Vacherot F, de la Taille A. Androgenic hormones and the excess male mortality observed in COVID-19 patients: new convergent data. *World J Urol* 2020;1:.
- [12] Wang X, Dhindsa R, Povysil G, Zoghbi A, Motelow J, Hostyk J, et al. TMPRSS2 transcriptional inhibition as a therapeutic strategy for COVID-19. 2020.

Mona Alshahawy*

Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

Mohamed Raslan^{a,b}

^a*Department of Clinical Research and Bio Analysis, Drug Research Centre, Cairo, Egypt*

^b*Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt*

Nagwa Sabri

Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

* Corresponding author at: Building 13, Omar Bin Khattab St., Sefarat District, Nasr City, Cairo, Egypt.

E-mail addresses: mona.elshahawy@pharm.asu.edu.eg (M. Alshahawy),
mohamedraslan280@gmail.com (M. Raslan),
nagwa.sabri@pharma.asu.edu.eg (N. Sabri).

Received 4 August 2020

Available online 6 September 2020