

University of Groningen

Men more vulnerable to COVID-19

Sama, Izziah E.; Voors, Adriaan A.

Published in:
European Heart Journal

DOI:
[10.1093/eurheartj/ehaa526](https://doi.org/10.1093/eurheartj/ehaa526)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Sama, I. E., & Voors, A. A. (2020). Men more vulnerable to COVID-19: explained by ACE2 on the X chromosome? *European Heart Journal*, 41(32), 3096-3096. <https://doi.org/10.1093/eurheartj/ehaa526>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Men more vulnerable to COVID-19: explained by ACE2 on the X chromosome?

Iziah E. Sama  and Adriaan A. Voors *

Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Online publish-ahead-of-print 24 June 2020

This commentary refers to ‘ACE2 is on the X chromosome: could this explain COVID-19 gender differences?’, by E. Culebras and F. Hernández, 2020:41:3095.

The apparent superiority of women over men in not succumbing to COVID-19 is not completely understood. Therefore, examination of the sex-distinguishing genetics of angiotensin-converting enzyme 2 (ACE2), the host receptor that binds SARS coronaviruses, might help explain this sex disparity.

The ACE2 gene is located on the X chromosome and is expressed in various tissues, including the heart, kidneys, and testes.¹ Endogenous soluble ACE2 (found in the circulation) is shed from the cell membrane-bound form and the enzyme responsible for this shedding is ADAM17,^{2,3} which is also membrane anchored. We recently postulated that the co-expression of ACE2 and ADAM17 in the testes (Supplementary figures 5 and 6 in Sama et al.⁴) might partially explain why plasma ACE2 concentrations are higher in men than in women.⁴

We agree with the commentary by Culebras and Hernández⁵ that the mere occurrence of ACE2 on the X chromosome could also be important in explaining why men would suffer more from ACE2-related diseases than women. In general, based on gene dosage, men suffer more often from X-linked disease traits than do women.⁶

Future studies relating ACE2 levels to its genomic context, copy number variations, X-inactivation, and various co-morbidities and other (epi)genetic factors are required to improve our understanding

of the gender-based disparities in ACE2-related pathophysiology and its relationship to the COVID-19 pandemic.

Funding

This work was supported by a grant from the European Commission (FP7-242209-BIOSTAT-CHF).

Conflict of interest: none declared

References

1. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Acton S. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res* 2000;**87**:E1–E9.
2. Lambert DW, Yarski M, Warner FJ, Thornhill P, Parkin ET, Smith AI, Hooper NM, Turner AJ. Tumor necrosis factor- α convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). *J Biol Chem* 2005;**280**:30113–30119.
3. Iwata M, Silva Enciso JE, Greenberg BH. Selective and specific regulation of ectodomain shedding of angiotensin-converting enzyme 2 by tumor necrosis factor α -converting enzyme. *Am J Physiol Cell Physiol* 2009;**297**:C1318–C1329.
4. Sama IE, Ravera A, Santema BT, van Goor H, Ter Maaten JM, Cleland JGF, Rienstra M, Friedrich AW, Samani NJ, Ng LL, Dickstein K, Lang CC, Filippatos G, Anker SD, Ponikowski P, Metra M, van Veldhuisen DJ, Voors AA. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. *Eur Heart J* 2020;**41**:3097–3098.
5. Culebras E, Hernández F. ACE2 is on the X chromosome: could this explain COVID-19 gender differences? *Eur Heart J* 2020;**41**:3095.
6. Migeon BR. X-linked diseases: susceptible females. *Genet Med* 2020;doi: 10.1038/s41436-020-0779-4.

*Corresponding author. Department of Cardiology, University Medical Center Groningen Hanzeplein 1, 9713 GZ, Groningen, The Netherlands. Tel: +31 50 3616161, Fax: +31 50 3618062, Email: a.a.voors@umcg.nl

© The Author(s) 2020. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com