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

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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 Hernández[5] 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.

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