Possible Pleiotropic Effect of *SRY* Gene May Increase Male Susceptibility to COVID-19

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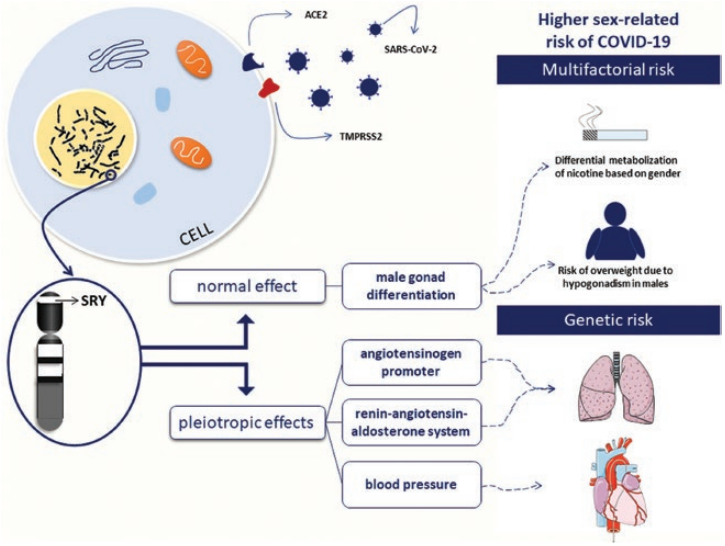
GRAPHICAL ABSTRACT



To the Editor: We have read with interest the manuscript entitled "SARS-CoV-2 Receptor ACE2 Gene Is Associated With Hypertension and Severity of COVID 19: Interaction With Sex, Obesity and Smoking," published in January 2021.

The authors[1] make extremely important contributions, especially on genetic predisposition to SARS-CoV-2. They investigated possible associations between genetic polymorphisms of ACE2 and patients with severe coronavirus disease. However, other genetic indicators may indicate a potential susceptibility mechanism for the severity of COVID-19 infection in men. Hormonal contributions can be partly responsible for sex disparities, but additional evidence points to sex chromosome contributions.

Importantly, the *SRY* (sex-determining region Y) gene in the Y chromosome (Yp11.2) works as a transcription factor for several genes. Studies of Y chromosome in animal models first suggested a *SRY* contribution to elevate blood pressure. *SRY* gene was found to be a positive regulator of the angiotensinogen promoter and a negative regulator of the *ACE2* promoter.[2] *ACE2* is located on the X chromosome (Xp22.2) and is one of the genes escaping X inactivation.

These findings indicate that *SRY* gene in the animal model modulates the renin–angiotensin–aldosterone system, a critical regulator of blood pressure, and the *ACE2* gene, indicating a sex-dependent activity. Moreover, *SRY* upregulates the renin promoter, while its homolog in the X chromosome, *SOX3* (SRY-related HMG-box 3) downregulates this promoter, thus affecting the renin–angiotensin–aldosterone system pathway.[3]

Interestingly, the results highlighted by Hamet *et al.*[1] indicate an association with ACE2 risk alleles and hypertension, which predispose males to severe COVID-19. Although further studies in humans can delineate whether such activity occurs in other species, several pleiotropic actions of the human *SRY* gene have been reported in the literature in the last decade.

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Recent studies described that smoking is a risk factor for cardiovascular disease and COVID-19 severity. Besides being implicated in sexual dimorphism, *SRY* gene is also involved in gonadal differentiation and male hormone production. Differences between sex hormones affect nicotine metabolism, some studies have shown that women metabolize nicotine faster than men. It may elevate ACE2 and transmembrane serine protease 2 (TMPRSS2) expression,[4] indicating gene–environment interactions, as described by Hamet *et al.*[1] Intriguingly, hormonal changes in adult men may result from hypogonadism, which contributes to various metabolic dysfunctions and can induce overweight.

ACE2 is widely expressed in multiple organs including lungs, heart, kidney, and also the adipose tissue. Obese men, especially those with exceeding visceral adipose tissue, could host higher viral load, contributing to development of more severe COVID-19. Early studies in male and female mice revealed sex differences in gene expression in adipose tissue. By recognizing genetic variabilities, in the future, we can better understand these differences in adipose pathophysiology. However, more studies are necessary to investigate the relationship between obesity and *SRY* gene.

In this context, research applying 3-dimensional structures or gene sequence analysis may contribute to indicate whether *SRY* gene exhibit variations in inhibition, modulating the renin–angiotensin–aldosterone system and whether gene expression imbalance predisposes SARS-CoV-2 interaction in males. Then, the study of sex differences may help to find appropriate therapies for all patients.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Hamet P, Pausova Z, Attaoua R, Hishmih C, Haloui M, Shin J, Paus T, Abrhamowicz M, Gaudet D, Santucci L, Kotchen TA, Cowley AW, Hussin J, Tremblay J. SARS-CoV-2 receptor ACE2 gene is associated with hypertension and severity of COVID 19: interaction with sex, obesity and smoking. *Am J Hypertens* 2021; 34:1–18).
2. Khan SI, Andrews KL, Jennings GL, Sampson AK, Chin-Dusting JPF. Y chromosome, hypertension and cardiovascular disease: is inflammation the answer? *Int J Mol Sci* 2019; 20:2892–2904.
3. 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; 21:1–23.
4. Gupta I, Sohail MU, Elzawawi KE, Amarah AH, Vranic S, Al-Asmakh M, Al Moustafa AE. SARS-CoV-2 infection and smoking: what is the association? A brief review. *Comput Struct Biotechnol J* 2021; 19:1654–1660.