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.

REFERENCES

1. Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study ($N = 4532$). *Ann Oncol*. 2020;31(8):1040-1045.
2. 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.
3. Altena E, Smeding R, van der Gaag KJ, et al. The Dutch Y-chromosomal landscape. *Eur J Hum Genet*. 2020;28:287-299.
4. Myres NM, Rootsi S, Lin AA, et al. A major Y-chromosome haplogroup R1b Holocene era founder effect in Central and Western Europe. *Eur J Hum Genet*. 2011;19:95-101.
5. Krementsov DN, Case LK, Dienz O, et al. Genetic variation in chromosome Y regulates susceptibility to influenza A virus infection. *Proc Natl Acad Sci U S A*. 2017;114:3491-3496.

Genetic and hormonal influence on SARS-CoV-2-infection susceptibility

Re: The potential influence of human Y-chromosome haplogroup on COVID-19 prevalence and mortality

We read with interest the correspondence by Delanghe et al.,[1] suggesting that genetic variants, and in particular Y chromosome polymorphisms, might explain outcome variations between genders. During the coronavirus disease 2019 (COVID-19) pandemic one prominent difference became apparent: men are more vulnerable to severe outcomes than women.[2] We recently published an observational study putting forward the hypothesis that male hormones may explain the increased male susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Our analysis was focused on SARS-CoV-2-infected prostate cancer patients of the Italian region of Veneto.

Importantly, as highlighted by Delanghe et al.,[1] the spread of the pandemic shows a marked geographical heterogeneity in the prevalence and mortality. Several factors can contribute to this phenomenon; the geographical distribution of genetic variants is one of them. Indeed, Delanghe et al.[1] reported a positive correlation between COVID-19 prevalence and mortality frequency and the frequency of the R1b-S116 haplotype in Europe. Noteworthy, several genes located on the Y chromosome have been associated with human diseases such as hypertension, coronary artery disease, and also infections. Indeed, several immune-related genes are on the Y chromosome and might modulate the immune response.[3]

Data from our study suggest that male hormones may be associated with increased SARS-CoV-2 susceptibility. It is important to highlight that the androgen receptor (*AR*) gene locus is located on the X chromosome, and that *AR* polymorphisms exist, which are linked to variable AR transcriptional activity. However, the association between *AR* genetic variants and COVID-19 severity has not been demonstrated yet.[4]

Other studies have investigated the influence of genetic factors in the spreading of SARS-CoV-2. *ACE2* and *TMPRSS2* are interesting target genes, as they are crucial for SARS-CoV-2 entry in infected cells.[5] Importantly, *ACE2* is located on the X chromosome and *TMPRSS2* is regulated by androgen levels. Asselta et al.[6] analyzed genetic variants of *ACE2* and *TMPRSS2* genes in the Italian population, looking for genetic factors underlying COVID-19 severity. According to their analysis, specific *TMPRSS2* genetic variants (one exonic variant and two distinct haplotypes) might be associated with more severe disease manifestations, and could also explain sex-related differences.[6]

Nevertheless, available data on the COVID-19 pandemic are not sufficient to confirm the existence of genetic modulators of SARS-CoV-2 infection outcomes. For this reason, there is an urgent need for large studies linking genetic variants with disease susceptibility and outcomes.

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DISCLOSURE

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REFERENCES

1. Delanghe JR, De Buzyere ML, De Bruyne S, Van Criekinge W, Speeckaert MM. The potential influence of human Y-chromosome haplogroup on COVID-19 prevalence and mortality. *Ann Oncol*. 2020;31(11):1582-1584.
2. Jin J-M, Bai P, He W, et al. Gender differences in patients with COVID-19: focus on severity and mortality. *Front Public Health*. 2020;8:152.
3. Maan AA, Eales J, Akbarov A, et al. The Y chromosome: a blueprint for men's health? *Eur J Hum Genet*. 2017;25(11):1181-1188.
4. McCoy J, Wambier CG, Vano-Galvan S, et al. Racial variations in COVID-19 deaths may be due to androgen receptor genetic variants associated with prostate cancer and androgenetic alopecia. Are anti-androgens a potential treatment for COVID-19? *J Cosmet Dermatol*. 2020;19(7):1542-1543.
5. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271-280.e8.
6. Asselta R, Paraboschi EM, Mantovani A, Duga S. ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. *Aging*. 2020;12(11):10087-10098.

Androgen deprivation therapy may constitute a more effective COVID-19 prophylactic than therapeutic strategy

Cellular transmembrane-serine-protease-2 (TMPRSS2), first cloned in 1997, has been intermittently the subject of intensive medical research, starting with the discovery of its role in recurrent TMPRSS2/ETS fusions and prostate cancer pathogenesis. TMPRSS2 protein was subsequently shown to proteolytically activate human respiratory tract viruses including influenza A, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV). Following the emergence of SARS-CoV-2 underlying the current coronavirus disease 2019 (COVID-19) pandemic, eyes naturally turned to the androgen-regulated *TMPRSS2* gene for SARS-CoV-2 lung tropism, mortality rates, and gender bias.

A study by Montopoli et al. in the *Annals of Oncology* reported findings congruent with the prevailing notion that high SARS-CoV-2 infection rates and disease severity in men may be the result of high androgen-driven *TMPRSS2* expression in the lungs. The authors posit that since *TMPRSS2* is under positive transcriptional control by the androgen receptor (AR), reduction of *TMPRSS2* expression following androgen deprivation therapy (ADT) in prostate cancer patients would be expected to correlate with reduced SARS-CoV-2 incidence, and in case of infection, with lesser disease severity.[1] While fewer prostate cancer patients undergoing ADT contracted the virus, androgen suppression did not lessen disease severity (Table 1).

Several findings indicate that TMPRSS2 is unlikely to play a major role in SARS-CoV-2 lung pathology in men (and women): first, modulation of SARS-CoV-2 by TMPRSS2 has so far been observed only in TMPRSS2 protein overexpression experiments and no patient data to this effect are available. Moreover, while high *TMPRSS2* mRNA levels have been documented in the human lung,[2] AR and TMPRSS2 proteins do not appear to be highly expressed in the lungs.[2,3] This indicates that androgens do not control *TMPRSS2* expression in the lungs and that while TMPRSS2 protease experimentally activates SARS-CoV-2 *in vitro*, it is probably not the host cell co-factor for SARS-CoV-2 lung infection in the clinical setting. In addition, recent studies showed no differences in *TMPRSS2* mRNA lung expression in men versus women[4] or male versus female mice,[4,5] further supporting a lack of androgen control of *TMPRSS2* expression in the lung or of a role for TMPRSS2 in mediating the increased SARS-CoV-2 incidence in men. Accordingly, ADT has no effect on *TMPRSS2* mRNA expression in mouse lungs,[4,5] further challenging the notion of a putative androgen—TMPRSS2 axis mediating SARS-CoV-2 gender bias and virulence. Another study, however, showed that ADT decreased *TMPRSS2* transcripts in murine lungs, though the same study showed that *TMPRSS2* lung expression is not reduced following castration.[6] Finally, *TMPRS22* transcripts are moderately modulated *in vitro* by androgens in the human lung adenocarcinoma cell line A549, raising the possibility of *TMPRSS2* transcript modulation by androgens in patients afflicted with lung adenocarcinoma.[5]

It is not completely clear from the study by Montopoli et al. if the reduced COVID-19 incidence in the ADT cohort is solely due to ADT, or whether it might be due to additional clinical variables inherent to the ADT group. In particular, disease stage and the type of treatment that may affect AR or TMPRSS2 expression and/or patients'

Table 1. Comparison of COVID-19 outcomes between prostate cancer patients undergoing (+ADT) or not (−ADT) androgen deprivation therapy (ADT)

Outcome	+ADT	−ADT
Hospitalizations	2 out of 4 (**50%**)	76 out of 114 (**66.7%**)
Mild disease	3 out of 4 (**75%**)	83 out of 114 (**72.8%**)
Severe disease	1 out of 4 (**25%**)	31 out of 114 (**27.2%**)
Admission to ICU	1 out of 4 (**25%**)	13 out of 114 (**11.4%**)
Deaths[a]	0 out of 4 (**0%**)	18 out of 114 (**15.8%**)

The current thinking posits that under ADT, expression of TMPRSS2 (a co-factor for SARS-CoV-2 activation and virulence) would be reduced in the lungs, leading to less severe disease, hospitalizations, ICU admissions, and deaths. Data in this table from the Italian Veneto region contradict this widely accepted supposition: ADT imparts no major positive effects on hospitalization, disease severity, or ICU admissions.
ICU, intensive care unit.
[a] A definitive analysis of mortality rates is rendered difficult owing to the very small size of the cohort of SARS-CoV-2-positive prostate cancer patients undergoing ADT (4 patients only). Nevertheless, if one were to assume that the fatality rates of the control group without ADT (~16%) are similar to those of the ADT group, one would predict less than one death in the latter, a finding consistent with the lack of fatalities in this group.