The American Osteopathic Society of Rheumatic Disease
and
The Integrative Health Alliance's

Weekly Educational Series

Genetic Snips and COVID-19 Severity

7-6-21

CHERYL ORTEL, M. D.,
M. S., F.A.C.O.G.

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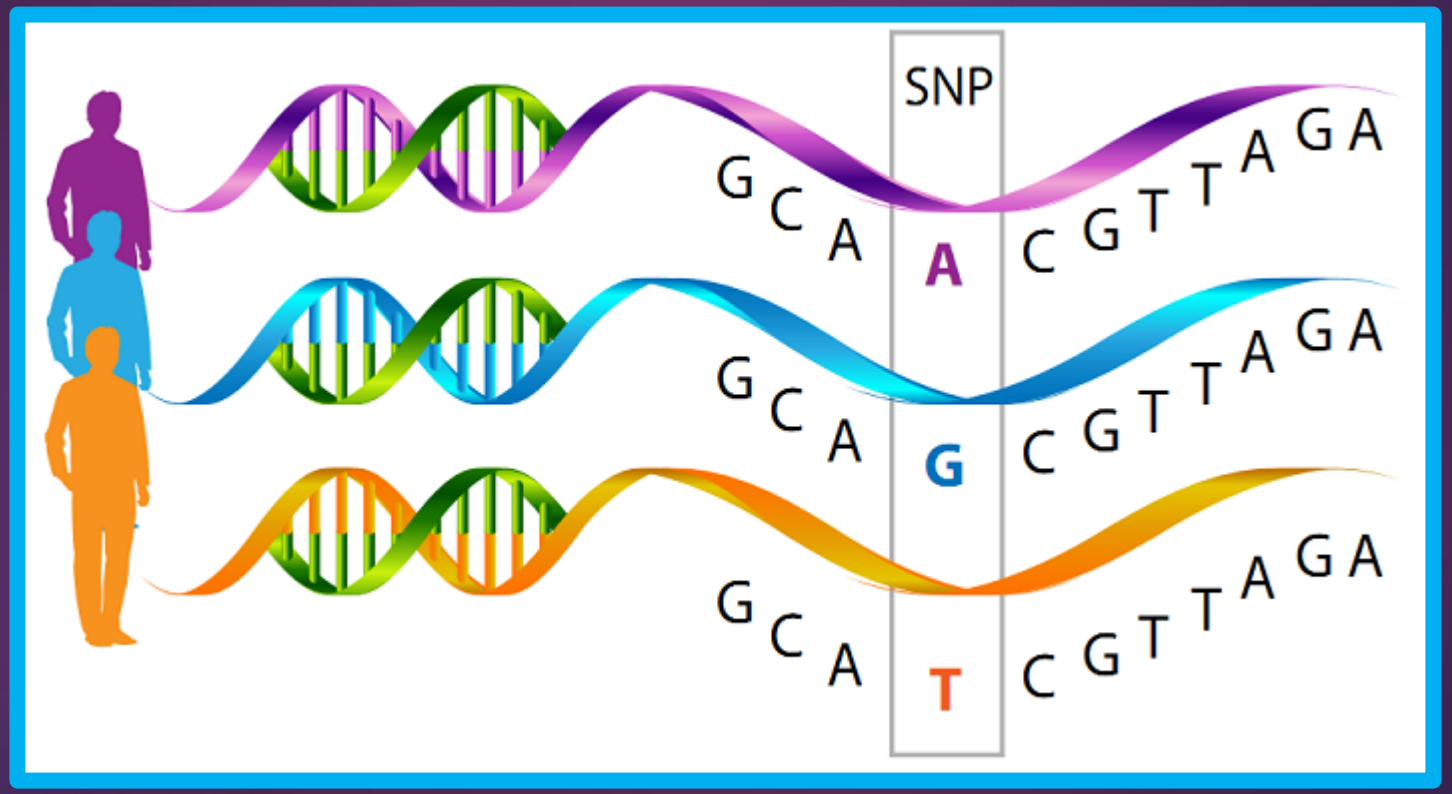
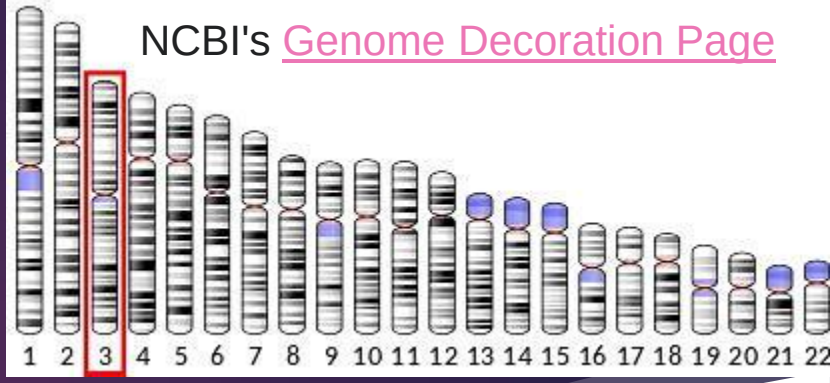
Genetic Polymorphisms and COVID-19



Dr. Cameron Troup MD in Genetics

CHROMOSOME 3 "Blood Type Gene"



- Chromosome 3 locus for blood-type gene + a stretch of DNA that acts as an **on-off switch for a gene producing a protein that triggers strong immune responses.**
- SARS-CoV-2 triggers overreaction of the immune system in some, leading to massive inflammation + lung damage —> via a **cytokine storm.**
- That loci has six genes, and it is not yet possible to say which of them influences the course of Covid-19.
- Genetic variations influence that response.

https://www.nature.com/articles/s41431-020-0636-6

ABO blood group locus & chromosome 3 gene cluster associated with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis (GWAS) (N=1,610)

8,582,968 single-nucleotide polymorphisms (SNPs) analyzed

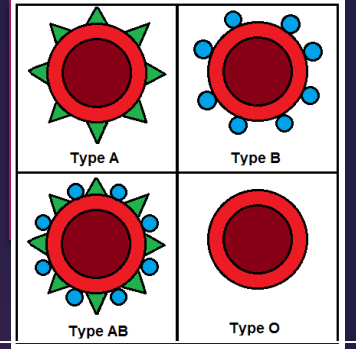
Type A blood linked to a 50 % increase in the likelihood of requiring oxygen or to going on a ventilator.

ACE2 genetic variants did not appear to make a difference in risk of severe Covid-19.

SNP (rs657152) at ABO locus is associated with elevated interleukin-6 (IL6) levels in childhood obesity.

https://www.medrxiv.org/content/10.1101/2020.05.31.20114991v1

ABO Blood Types - Meta analysis 7 studies

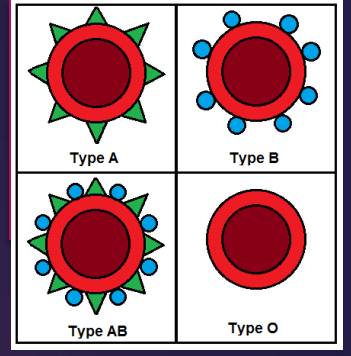


Netwellness.org

- **Blood group A** is associated with a higher risk of infection + serious illness.
- SARS-CoV-2 binds to ACE2, + ABO carbohydrates.
- Lack antigens on blood group O leads to less molecular contact with the virus + lower risk of infection.
- Blood group O has a lower ACE level. ACE is an enzyme that activates angiotensin. Lower levels of this enzyme can reduce the risk of hypertension which is a COVID-19 risk factor.
- Blood group O have higher interleukin 6 (IL-6). IL-6 is a proinflammatory cytokine that can be produced by many cells + has an important role in cell defense in acute phase.

https://www.medrxiv.org/content/10.1101/2020.06.07.20124610v1.full.pdf

Pooled Frequency of ABO Blood Types- Meta analysis of 7 studies on COVID-19



Netwellness.org

BLOOD TYPE	A	B	AB	O
PERCENT (%) COVID-19	36.22	24.99	29.6	9.29
% FATAL CASES	40	23	29	8
ODDS RATIO	1,16 (CI 95%:1.02-1.33		1.25 (CI 95% :0.84-1.86)	0.73(CI 95%: 0.60-0.88
Blood Type	**A**	**B**	**AB**	**O**
CHINA %	**28** (-> 63% of positives)	**19**	**5**	**48**
USA %	**41**	**11**	**4**	**44**

https://www.medrxiv.org/content/10.1101/2020.06.07.20124610v1.full.pdf
https://en.wikipedia.org/wiki/Blood_type_distribution_by_country

Major papers to be covered

1. **New insights into genetic susceptibility of COVID-19: an *ACE2* and *TMPRSS2* polymorphism analysis** Published: 15 July 2020
https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01673-z

2. **Angiotensin-converting enzymes (*ACE*, *ACE2*) gene variants and COVID-19 outcome** Published online 2020 Aug 31
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456966/#s0040title

3. **Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019** Published online 2020 Jul 29
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7387924/

4. **ACE gene variants rise the risk of severe COVID-19 in patients with hypertension, dyslipidemia or diabetes. A pilot study** Posted March 26, 2021.
https://www.medrxiv.org/content/10.1101/2021.03.24.21253576v1

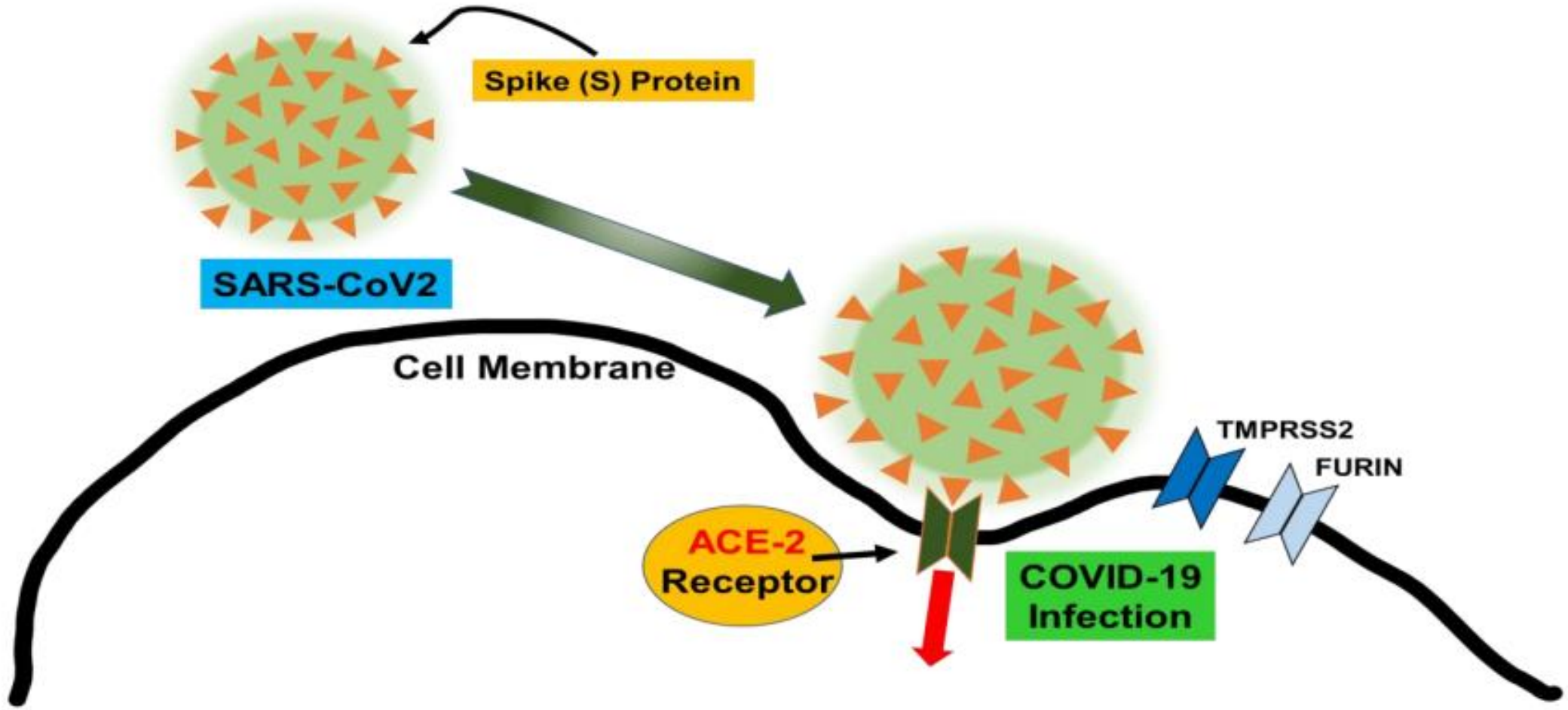
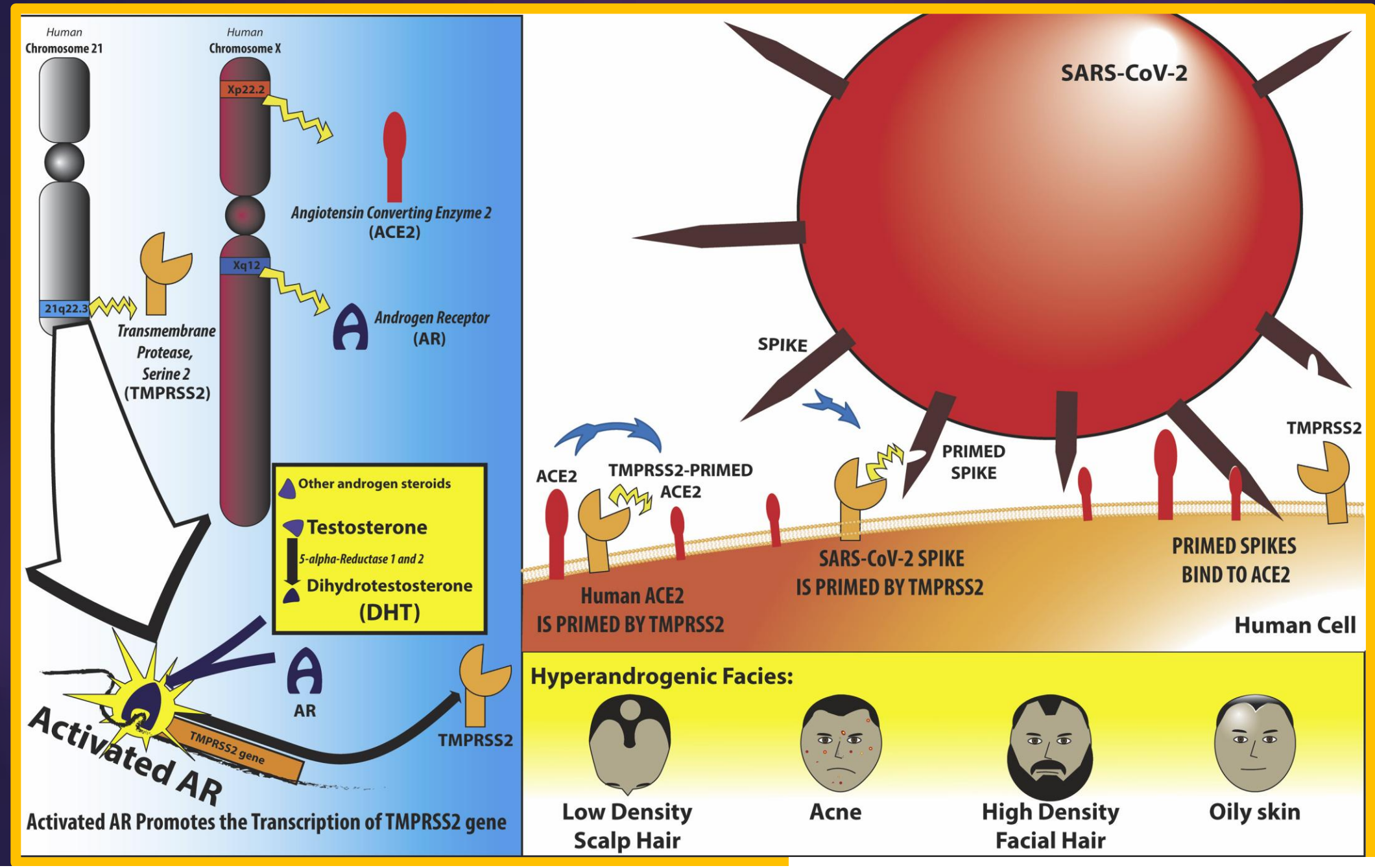


Figure 1. This represents the spike protein of the COVD-19 virus. The spike enters the cell through the ACE-2 receptor. The spike is subsequently cleaved by the following proteases, transmembrane serine protease 2 (TMPRSS2), and FURIN, creating an active COVID-19 infection.

Heme oxygenase-1(HO-1).

Genetic Polymorphisms Complicate COVID-19 Therapy: Pivotal Role of HO-1 in Cytokine Storm



TMPRSS2 enzyme primes the spike protein for attachment to ACE2 Receptor + is androgen activated

Journal of the American Academy of Dermatology DOI: (10.1016/j.jaad.2020.04.032)

Interferon-induced transmembrane protein 3 SNP rs12252-C is associated with disease severity in COVID-19

Chromosome 11

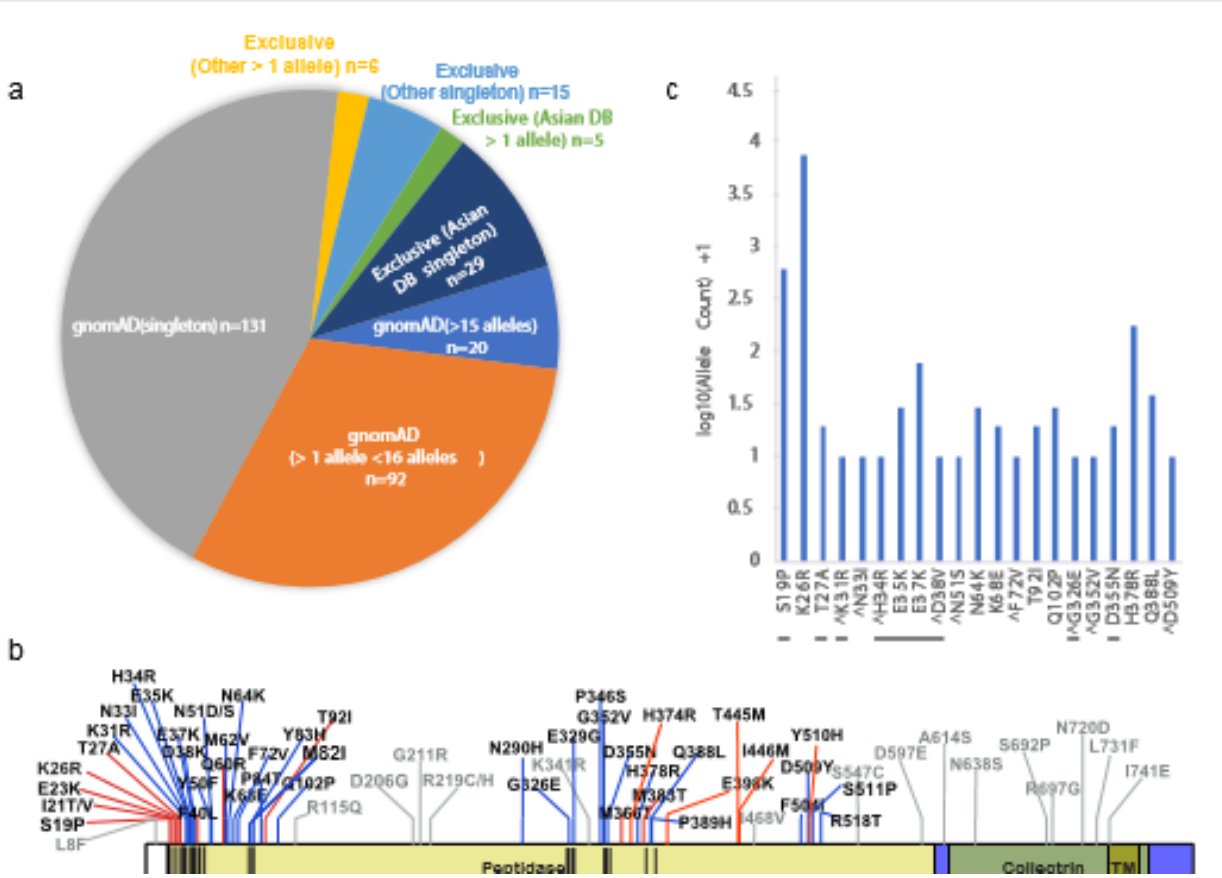
- **Homozygosity for the C allele of rs12252** in the **interferon-induced transmembrane protein 3 (*IFITM3*) gene** is associated with more **severe** disease in an **age dependent** manner.
- Association of IFITM3 rs12252 polymorphisms, with mild flu in an Iranian (Fars) population- susceptibility to several viral infections, such as West Nile virus, dengue virus, rhinovirus, corona virus, HIV, respiratory syncytial virus, and influenza A virus.
- rs12252 Found in 0% Japanese, 44% Chinese, esp. Han, 5.4% in Northern Europeans,+ UK Caucasians

The Journal of Infectious Diseases, jiaa224, https://doi.org/10.1093/infdis/jiaa224 **Published:** 29 April 2020
DOI: 10.1186/s12985-017-0884-4

ACE2 receptor polymorphisms predict SARS-CoV-2 susceptibility ACE2

BAD--> ACE2 variants S19P, I21V, E23K, K26R, T27A, N64K, T92I, Q102P and H378R are predicted to increase susceptibility

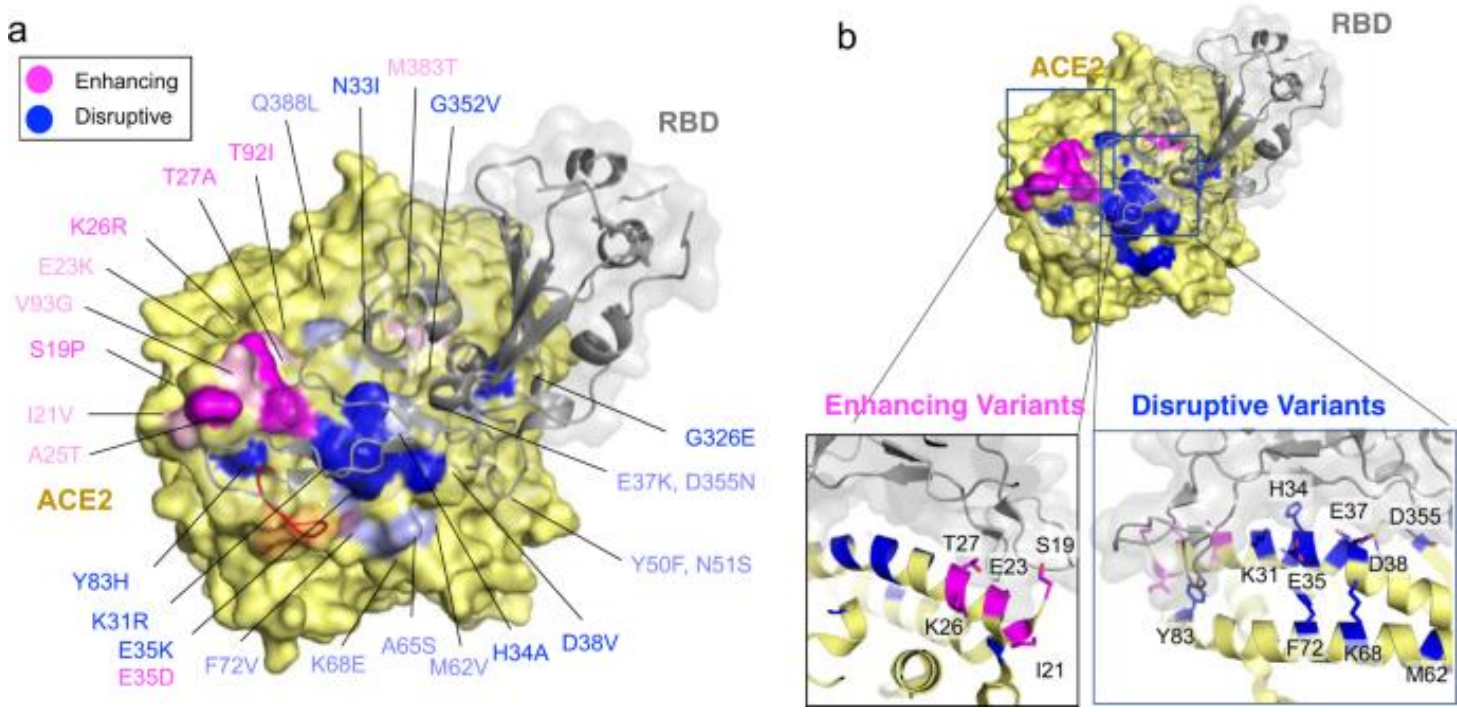
GOOD-- >ACE2 variants K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L + D509Y are putative protective variants predicted to show decreased binding to SARS-CoV-2 S-protein



Communications Biology doi: 10.1038/s42003-021-02030-3

ACE2 receptor polymorphisms predict SARS-CoV-2 susceptibility ACE2

- Residues in ACE2 showing polymorphic variation in human populations were mapped on to the structure of the ACE2/SARS-CoV-2 RBD (PDB: 6VW1) and colored according to their effect on the predicted affinity to SARS-CoV-2 RBD. Polymorphisms that were predicted to enhance the binding between ACE2 + S-protein are magenta.
- Polymorphisms that are predicted to disrupt the binding between ACE2 + S-protein are dark blue.
- Variable loop in the ridge binding motif consisting of residues V483 and E484 is red.
- Region in the structure (PDB: 6LZG) is zoomed-in to show variants predicted to enhance or disrupt the ACE2 – SARS-CoV-2 interaction.



Communications Biology doi: 10.1038/s42003-021-02030-3

New insights into genetic susceptibility of COVID-19: an *ACE2* and *TMPRSS2* polymorphism analysis

- Infection depends on host cell factors angiotensin-converting enzyme 2 (ACE2) for entry into cells + host transmembrane serine protease TMPRSS2 for SARS-CoV-2 spike (S) protein priming.
- ACE2, encoded on X-chromosome, catalyzes conversion of angiotensin II to angiotensin-(1–7), which acts as a vasodilator + exerts important modulatory effects on the cardiovascular system.
- *TMPRSS2* is a key gene in prostate cancer, as an associated translocation drives ETS-family oncogene expression in a large proportion of tumors. Expression *ACE2* + *TMPRSS2* are likely to dictate SARS-CoV-2 tissue tropism.
- Incidence + mortality rates are significantly different between male and female COVID-19 patients, + disease is associated with pre-existing conditions, such as cancer and cardiovascular disorders, in particular individuals with hypertension receiving anti-hypertensive medications.

New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis | BMC Medicine | Full Text (biomedcentral.com)

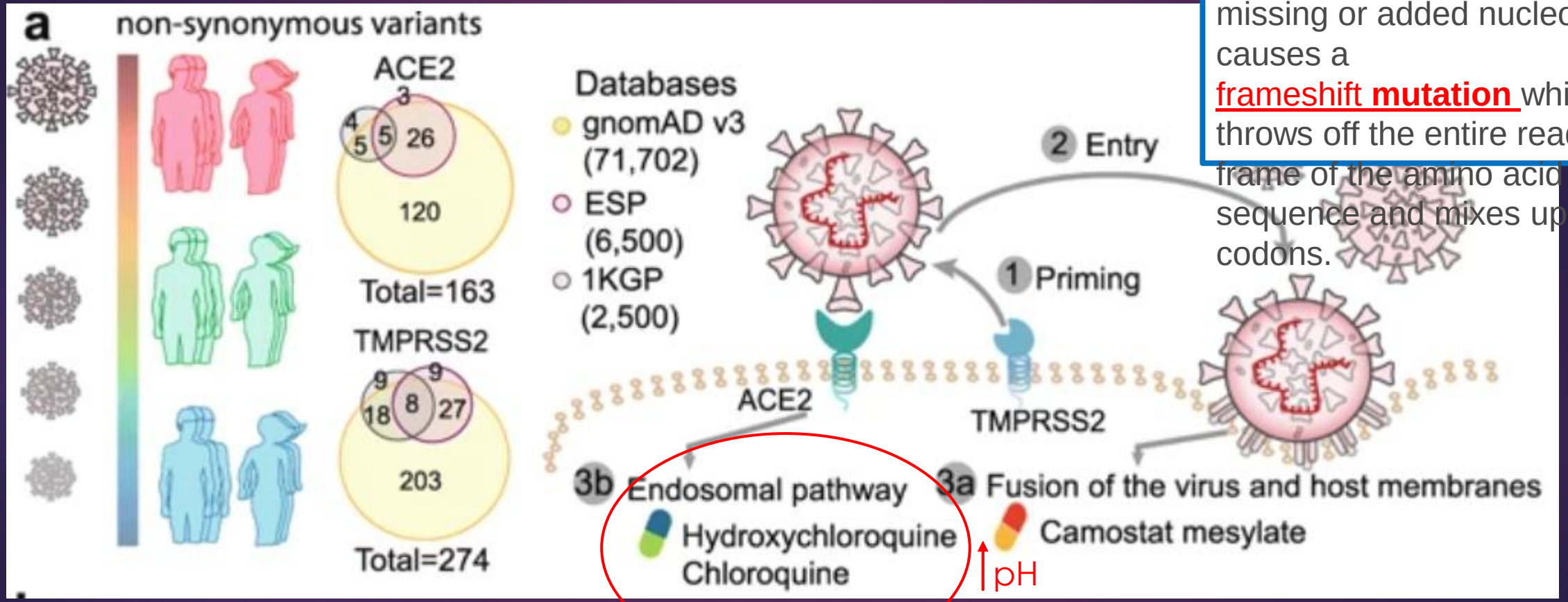
New insights into genetic susceptibility of COVID-19: an *ACE2* and *TMPRSS2* polymorphism analysis

- *ACE2* polymorphisms were found to be associated with cardiovascular and pulmonary conditions by altering the angiotensinogen-ACE2 interactions, such as p.Arg514Gly in the African/African-American population.
- Unique but prevalent polymorphisms (including p.Val160Met (rs12329760), an expression quantitative trait locus (eQTL)) in *TMPRSS2*, offer potential explanations for differential genetic susceptibility to COVID-19 as well as for risk factors, including those with cancer and the high-risk group of male patients.
- Polymorphisms in *ACE2* or *TMPRSS2* could guide effective treatments (i.e., hydroxychloroquine and camostat) for COVID-19.

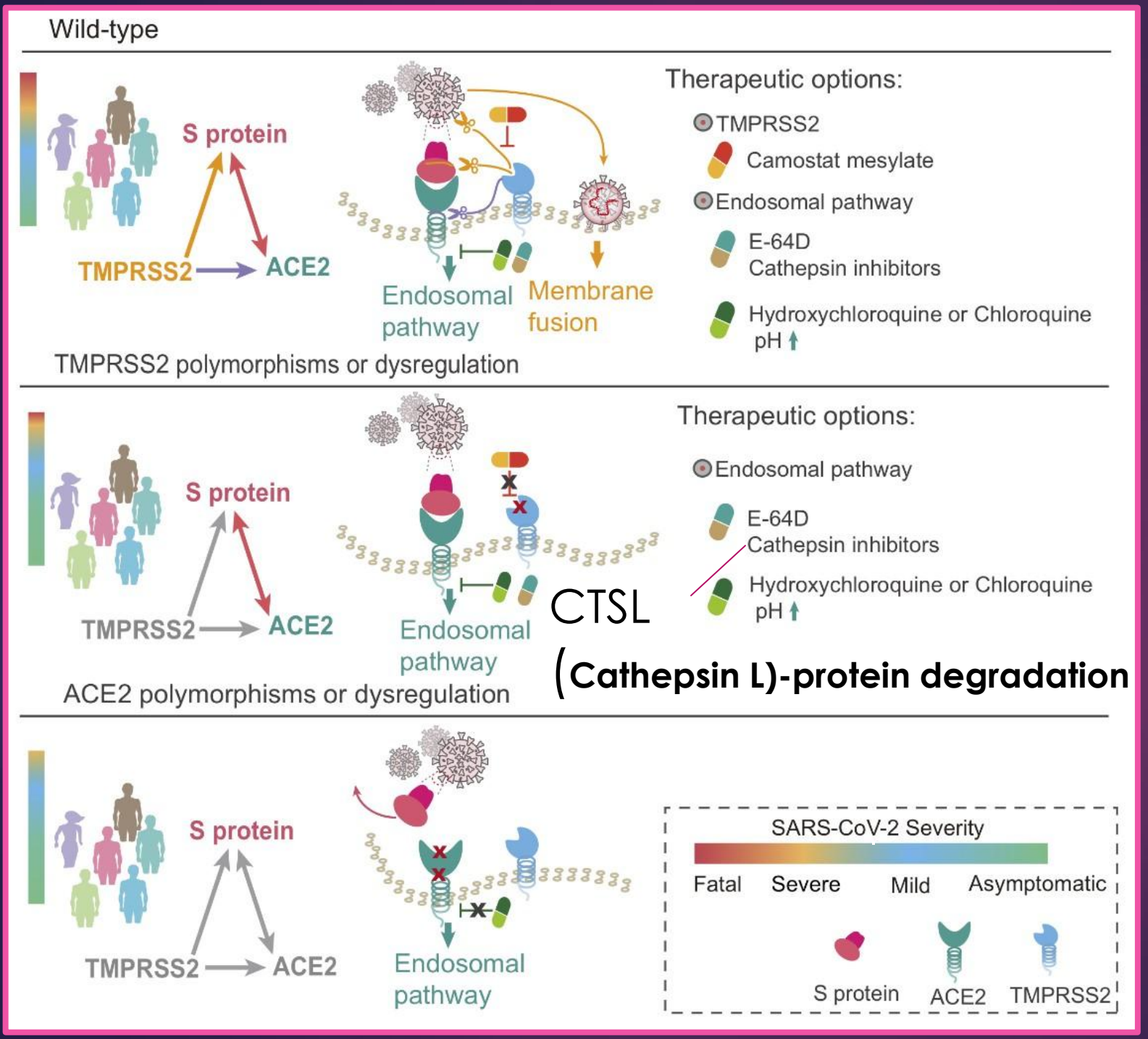
New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis | BMC Medicine | Full Text (biomedcentral.com)

New insights into genetic susceptibility of COVID-19:
& *ACE2* and *TMPRSS2* polymorphisms

Nonsynonymous mutation: there is an insertion or deletion of a single nucleotide in the sequence during transcription when the messenger RNA is copying the DNA. This single missing or added nucleotide causes a frameshift **mutation** which throws off the entire reading frame of the amino acid sequence and mixes up the codons.



https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01673-z Previously presented as a preprint



Pharmacogenomics model of potential combination therapies

(Hydroxychloroquine, E-64D (a protease inhibitor), + camostat mesylate (an approved TMPRSS2 for treatment for chronic pancreatitis in Japan)) for COVID-19 by blocking ACE2 + TMPRSS2 across different populations with 3 genotypes.

https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01673-z

Populations at risk

Average of six genetic variants associated with higher ratios of ACE2 cells: rs233575 (A), rs714205 (G), rs1978124 (C), rs879922 (G), rs2048683 (G), rs1877752 (C)

Code	Population	%
JPT	Japanese in Tokyo, Japan	92%
CHS	Southern Han Chinese	92%
EAS	*East Asian*	91%
KHV	Kinh in Ho Chi Minh City, Vietnam	91%
CHB	Han Chinese in Beijing, China	90%
CDX	Chinese Dai in Xishuangbanna, China	90%
PEL	Peruvians from Lima, Peru	78%
BEB	Bengali from Bangladesh	77%
STU	Sri Lankan Tamil from the UK	75%
ITU	Indian Telugu from the UK	74%
MXL	Mexican Ancestry from Los Angeles USA	72%
SAS	*South Asian*	72%
GIH	Gujarati Indian from Houston, Texas	68%
AMR	*Admixed American*	66%
ASW	Americans of African Ancestry in SW USA	66%
PJL	Punjabi from Lahore, Pakistan	65%
ACB	African Caribbeans in Barbados	64%
LWK	Luhya in Webuye, Kenya	63%
MSL	Mende in Sierra Leone	62%
AFR	*African*	62%
ESN	Esan in Nigeria	62%
GBR	British in England and Scotland	61%
GWD	Gambian in Western Divisions in the Gambia	61%
PUR	Puerto Ricans from Puerto Rico	60%
CLM	Colombians from Medellin, Colombia	59%
YRI	Yoruba in Ibadan, Nigeria	57%
FIN	Finnish in Finland	57%
IBS	Iberian Population in Spain	56%
EUR	*European*	56%
CEU	Utah Residents with Northern and Western European Ancestry	53%
TSI	Toscani in Italia	51%

1000 Genomes Project

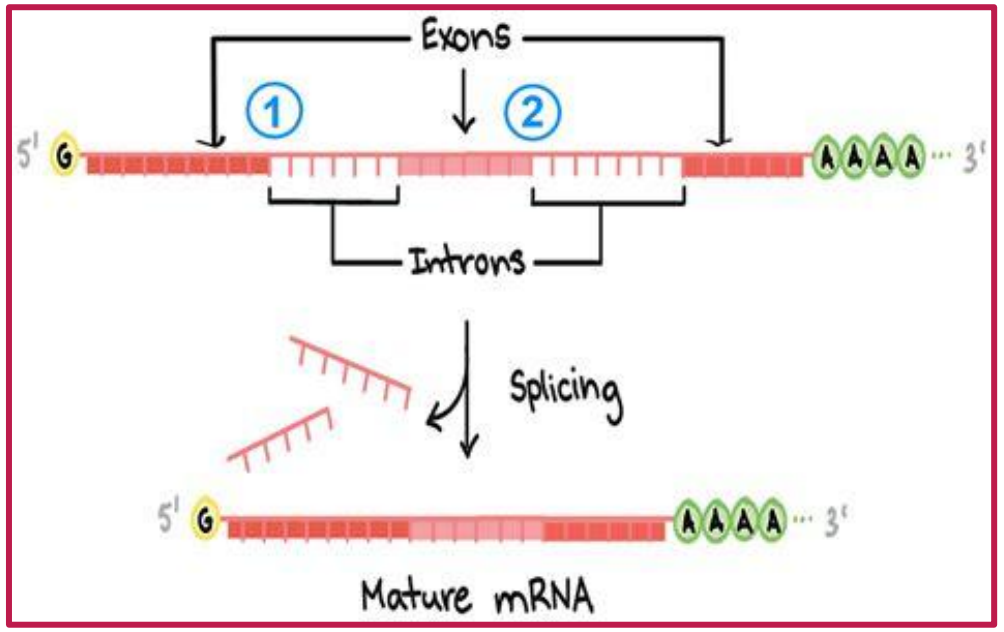
Populations most at risk

Genetic variants associated with higher ratios of ACE2 cells:

- East Asians, Japanese, + Han Chinese are most likely to become severely sick with exposure. > 90%.
- Africans ~60% range, considered low to medium.
- Europeans ~50%.

https://img.auctiva.com/imgdata/1/9/6/8/1/0/0/webimg/1051684762_o.jpg

INTRONS are Removed by splicing from raw RNA copy of a gene.

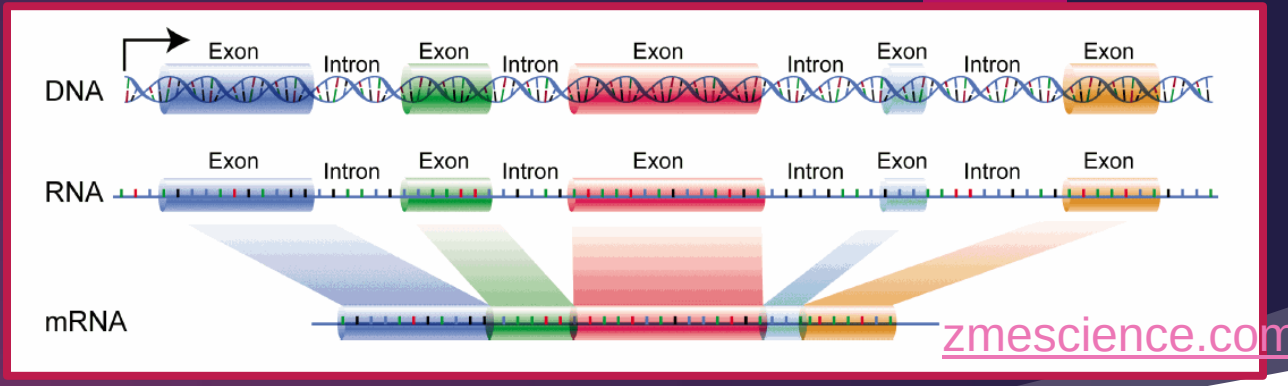


INTRONS – removed from the final mRNA.
>200,000 introns in the genome.
Small changes can impair slicing causing faulty proteins.
~14% of single letter mutations have been linked to human disease occur with DNA sequences that flag intron positions in the genome.

EXONS – Protein –coding regions.

https://www.cshl.edu/predicting-how-splicing-errors-impact-disease-risk/

ACE gene locations



- ACE-1 gene is located on the long arm of chromosome 17. Mutations in the ACE gene have been associated with a severe form of the renal disease called renal tubular dysgenesis.
- Rigat et al. showed the level of circulating ACE enzymes depends on the insertion/deletion (I/D) polymorphism of a 287-bp element on **intron** 16 on **chromosome 17.** (Intron is a segment of DNA or RNA which does not code for proteins and interrupts the sequence of genes.)
- *ACE2* gene is located on the X chromosome (location: Xp22.2; nucleotides 15 494 402–15 602 148, GRCh38.hg38 version).
- ***ACE2* sequencing showed no coding sequence variants** that could explain an increased risk of developing COVID-19.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456966/#s0040title

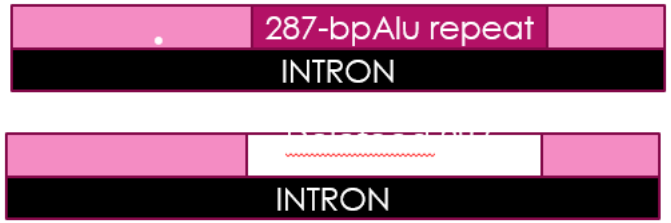
Retained introns are associated with cancer

ACE Gene Polymorphism and Acute Lung Injury

- ACE gene polymorphism is characterized by insertion (*I*) or deletion (*D*) of a 287-bp Alu repeat sequence in intron 16 of the ACE gene. Introns are eliminated by splicing before the final product.
- Insertion/deletion (*I*/*D*) polymorphism is associated with circulating + tissue ACE levels, determines ~1/2 serum ACE level variability in general population, where *D* allele is associated with higher ACE activity. Mean ACE activity levels in *DD* carriers were ~2X's that in *II* genotype individuals. ACE gene polymorphism may play an important role in COVID-19 patients who are susceptible to severe lung injury or ARDS.
- Evidence supporting the relationship of ACE *I/D* polymorphism + clinical outcome of ARDS exists.

In 1 study, the 28 day mortality rates for ACE *I/D* Genotypes:

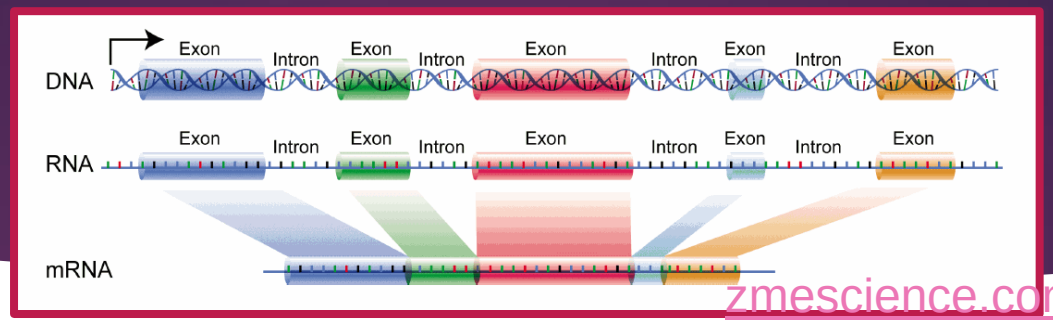
II - 42% Best survival
ID - 65%
DD- 75% ARDS, death >5 Xs*



- Patients with *II* genotype have a better survival than those with non-*II* genotypes. In another study, the *DD* genotype frequency is higher in patients with ARDS and is significantly associated with mortality. In a prospective study of ARDS, increased mortality of **>5X's*** is found in patients with a homozygous *DD* genotype compared with the *II* genotype."

Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019 (nih.gov)

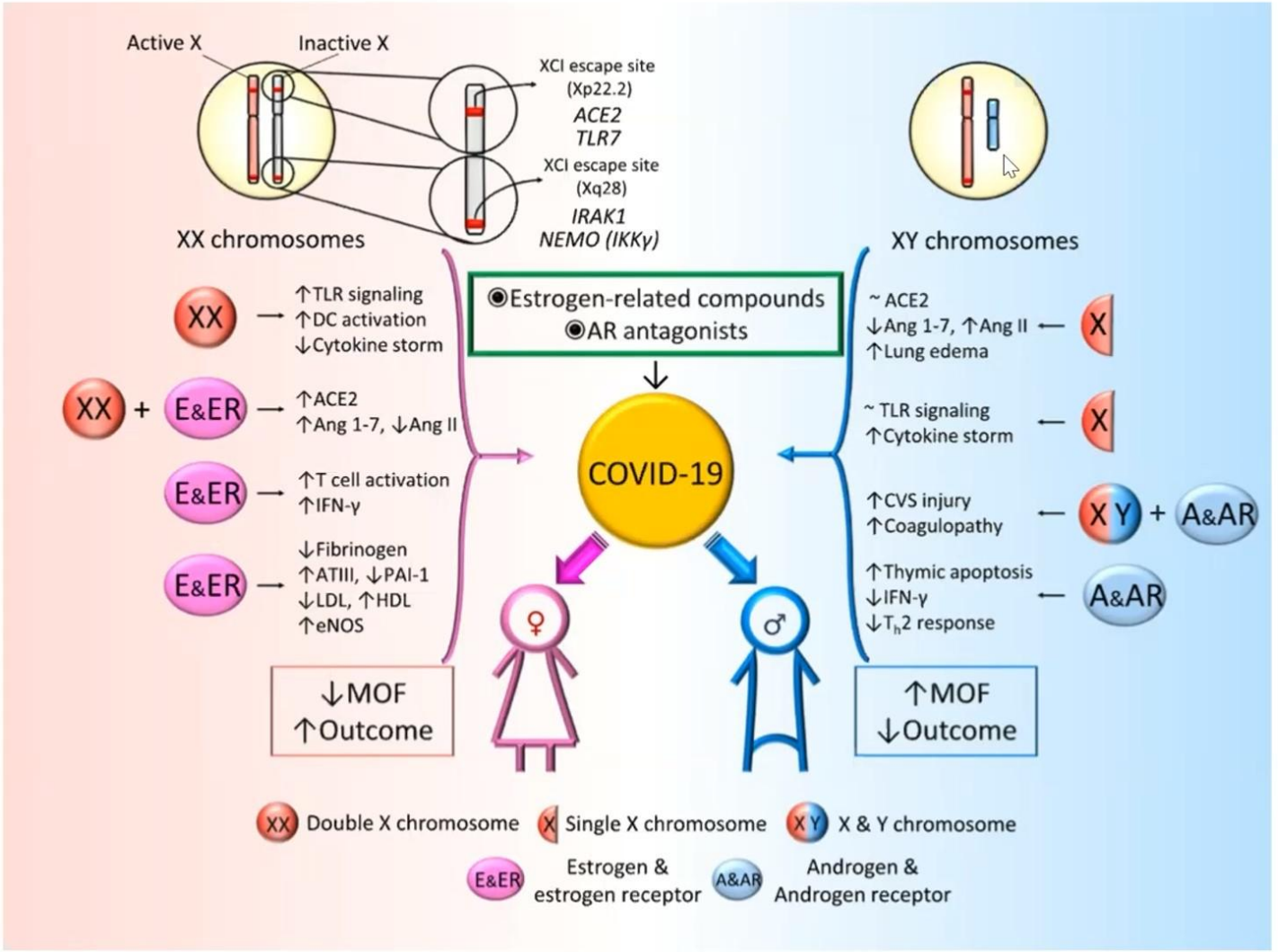
Racial differences of ACE gene polymorphisms



- USA : AA have highest frequency of *D* allele (89%) when compared with Indians (69%) + whites (69%).
- Europe: Italy, Spain, + France have high frequency of *D* allele up to 82% to 87%. Asia, the Eastern Asian populations, (Chinese, Korean, Taiwanese, and Japanese), have a high frequency of ACE gene *II* allele, which is reportedly higher than the European populations (33% to 51% versus 13-27%).
- Racial variance of ACE *I/D* genotype coincides different outcomes-> populations with high frequency of *D* alleles seem to experience higher fatality.
- African Americans have a disproportionately high fatality rate in the United States. Patients from Italy, Spain, + France also experience a high fatality in Europe.
- Low frequency of ACE *D/D* and high frequency of *II* genotype seen in Asians populations seem to be associated with relatively low fatality of COVID-19 in those nations.

Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019 (nih.gov)

ACE2 on X chromosome



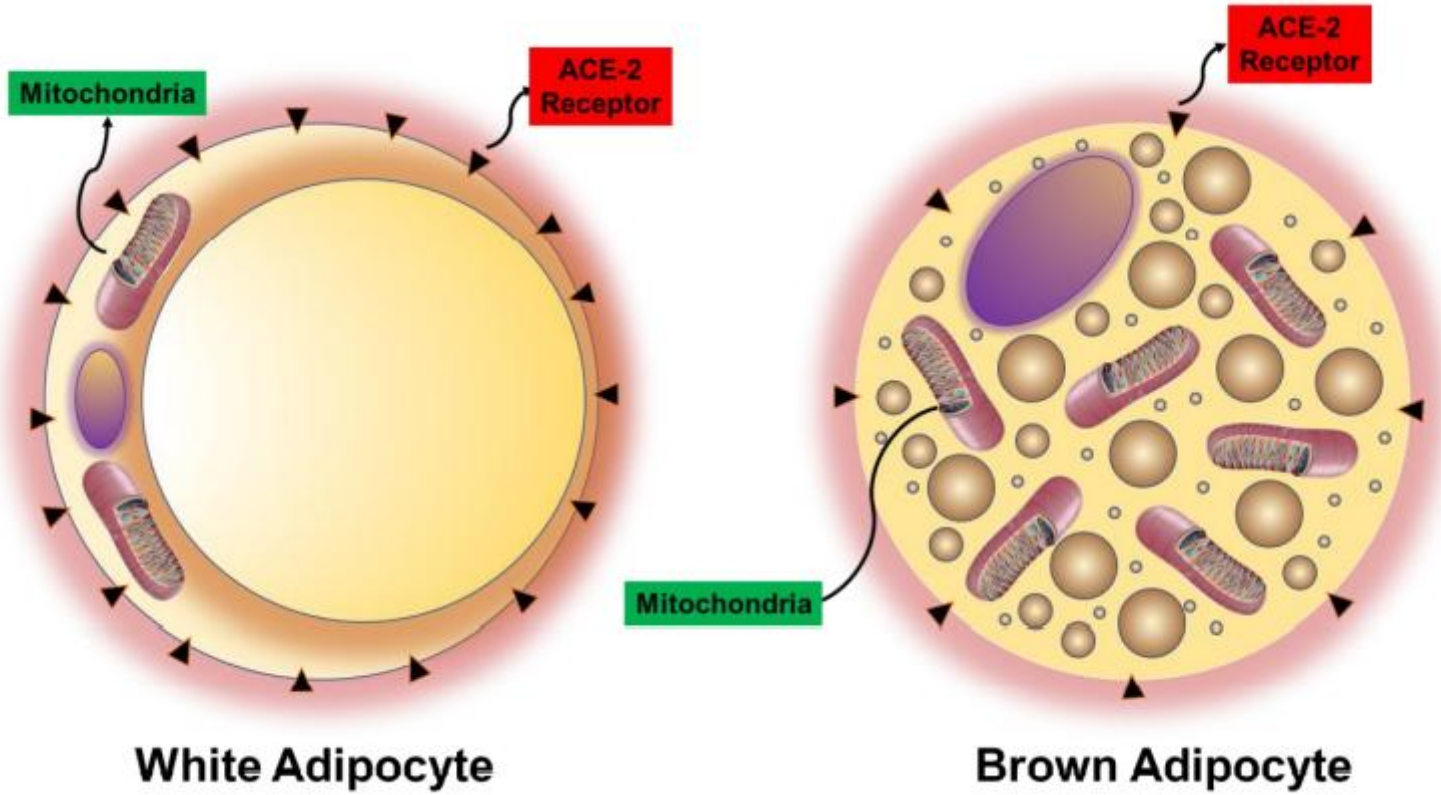
Li *et al. Critical Care* (2020) 24:405

Angiotensin-converting enzymes (*ACE*, *ACE2*) gene variants and COVID-19 outcome

- Expression of *ACE2* gene can regulate susceptibility to infection. Balance between ACE1 and ACE2 activity has been implicated in the pathogenesis of respiratory diseases and plays a role in the severity of COVID-19.
- Functional *ACE1*/*ACE2* gene polymorphisms have been associated with the risk of cardiovascular + pulmonary diseases, + contribute to COVID-19 outcomes.
- 204 COVID-19 patients (137 non-severe and 67 severe-ICU cases) and 536 age-matched controls. *ACE1* insertion/deletion + *ACE2* rs2285666 polymorphism were determined. Variable frequencies were compared between groups.
- Adverse outcomes of COVID-19 are associated with male gender, hypertension, hypercholesterolemia and *ACE1* genotype.
- *ACE1*-I/D might influence COVID-19 severity, but the effect was dependent on hypertensive status.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456966/#s0040title

ACE2 overexpressed in obesity and diabetes allows COVID-19 to infect the cell



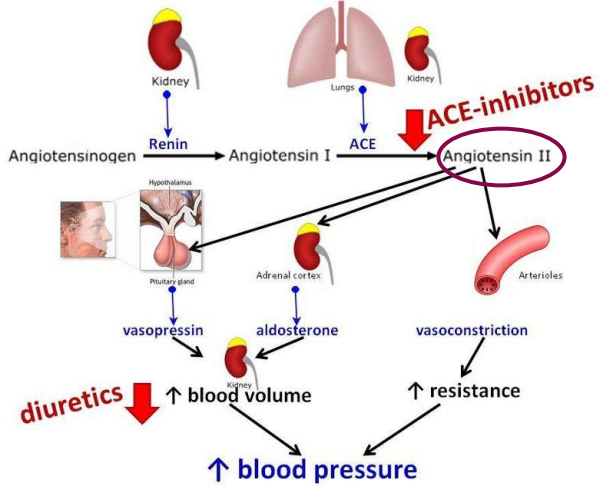
White Adipocyte - Obese tissue has low mitochondria and HO-1, resulting in high ROS and upregulation of ACE-2 receptors.

Brown Adipocyte -has high amounts of mitochondria and HO-1 that results in low ROS. Brown is better than white adipose tissue in its ability to handle inflammation caused by COVID-19.

Genetic Polymorphisms Complicate COVID-19 Therapy: Pivotal Role of HO-1 in Cytokine Storm

Angiotensin II and Acute Lung Injury-

Hypothesis of Renin-Angiotensin System (RAS) imbalance is mainly based on the **reduction of membrane-bound ACE2** as a consequence of enzyme endocytosis complex with the S protein of the virus.



Imbalance between ACE + ACE2 + increased ATII play a significant pathologic role in acute lung injury.

In influenza animal models, reduced ACE2 expression is associated with severe lung injury.

Binding SARS-CoV to mouse ACE2 *in vivo* causes reduced ACE2 expression + greater acute lung injury.

Mouse model - where the lung injury is induced by high-volume ventilation, there appears to be an increased lung injury related to the overproduction of lung ATII.

Humans - serum ATII level is elevated in patients with ARDS and sepsis, [+] where microvascular reoxygenation rate + plasma ATII level are inversely associated.

In a small cohort of COVID-19 patients, plasma ATII levels are markedly elevated compared with healthy controls and are linearly correlated with viral load and the severity of lung injury, suggesting a **systemic RAS imbalance as a result of ACE2 down-regulation from SARS-CoV-2 infection.**

Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019 (nih.gov)

ACE2 rs2285666 variant associated with hypertension in an elderly population, without significant difference between mild and severe COVID-19 patients.

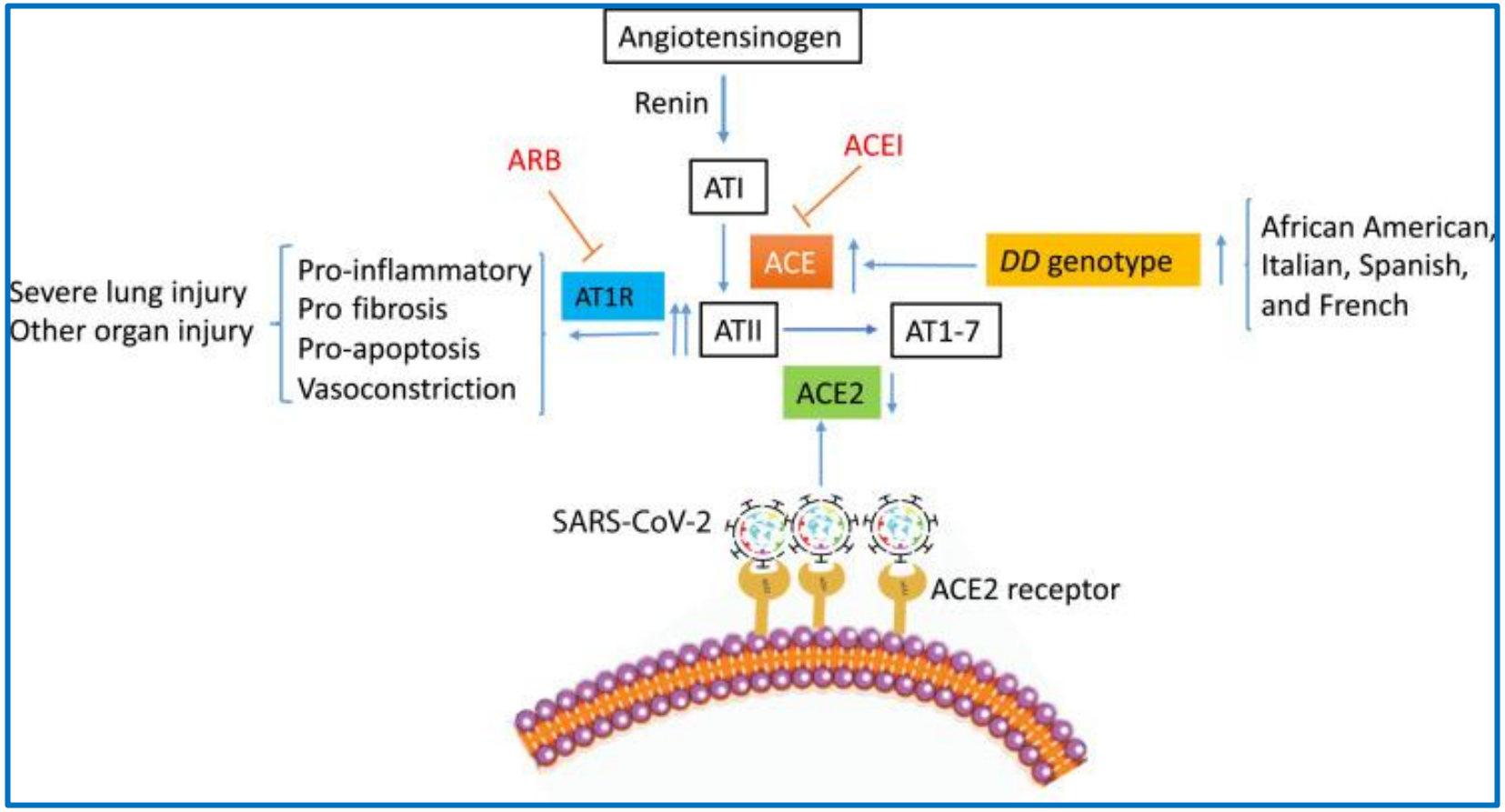
On X Chromosome

- ACE2 expression in lungs markedly decreases with age and is greater in men than in women.
- Reduced ACE2 expression increases risk for hypertension, cardiac hypertrophy, + heart failure.
- High activity of ACE would increase the risk of lung + cardiovascular disease by increased activity of the Ang-II/AT1R axis.
  - Common variants in the 2 *ACE* genes have been associated with the risk of hypertension, heart disease, renal failure, and pulmonary disease.
- Individuals with a D/D genotype showed the highest blood ACE levels, and this increased expression would explain the higher risk for cardiovascular and respiratory disease among individuals who are deletion-homozygous.

- This polymorphism has been related with the outcome in acute respiratory distress syndrome (ARDS) by some authors, and with progression of pneumonia in SARS

Angiotensin-converting enzymes (ACE, ACE2) gene variants and COVID-19 outcome (nih.gov)

Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019



Impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on metabolic pathways driven by angiotensin-converting enzyme (ACE) + ACE2 in the renin-angiotensin system,
Proposed mechanisms of ACE *DD* genotype in severe lung injury of coronavirus disease 2019, and potential impact of ACE *DD* genotype in high-risk population.
Potential therapeutic targets for ACE inhibitors (ACEIs) + angiotensin (AT) 1 receptor blockers (ARBs).

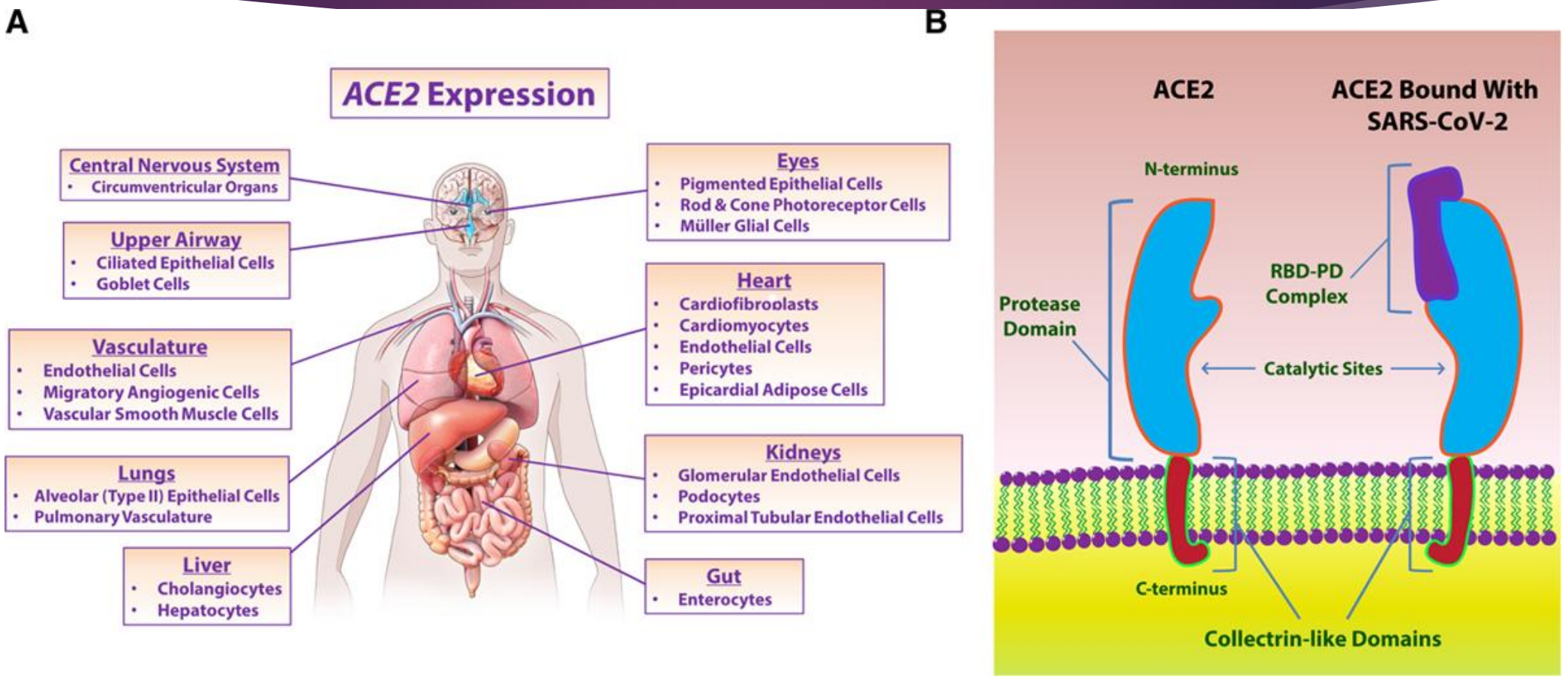
Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019 (nih.gov)

ACE gene polymorphism and the disease severity has been investigated in SARS

- Investigated in SARS, which caused an outbreak in 2002 that affected >8000 individuals and resulted in 774 deaths worldwide (World Health Organization, *last accessed June 20, 2021), with mixed results.
- Frequency of ACE gene *D* allele is significantly higher in the **hypoxemic** group than in nonhypoxemic group in a small study. A later study failed to show a significant association of ACE polymorphism with the pulmonary disease severity in the SARS patients.
- It is plausible that the severity of acute lung injury of COVID-19 is influenced to some extent by the genotypes of ACE *I/D* polymorphism. Likely, genetic susceptibility of severe lung injury from SARS-CoV-2 infection is complex and mediated by multiple genes.
- A large genome-wide association study has reported a novel susceptibility locus associated with ABO blood group in COVID-19 patients with severe lung injury.

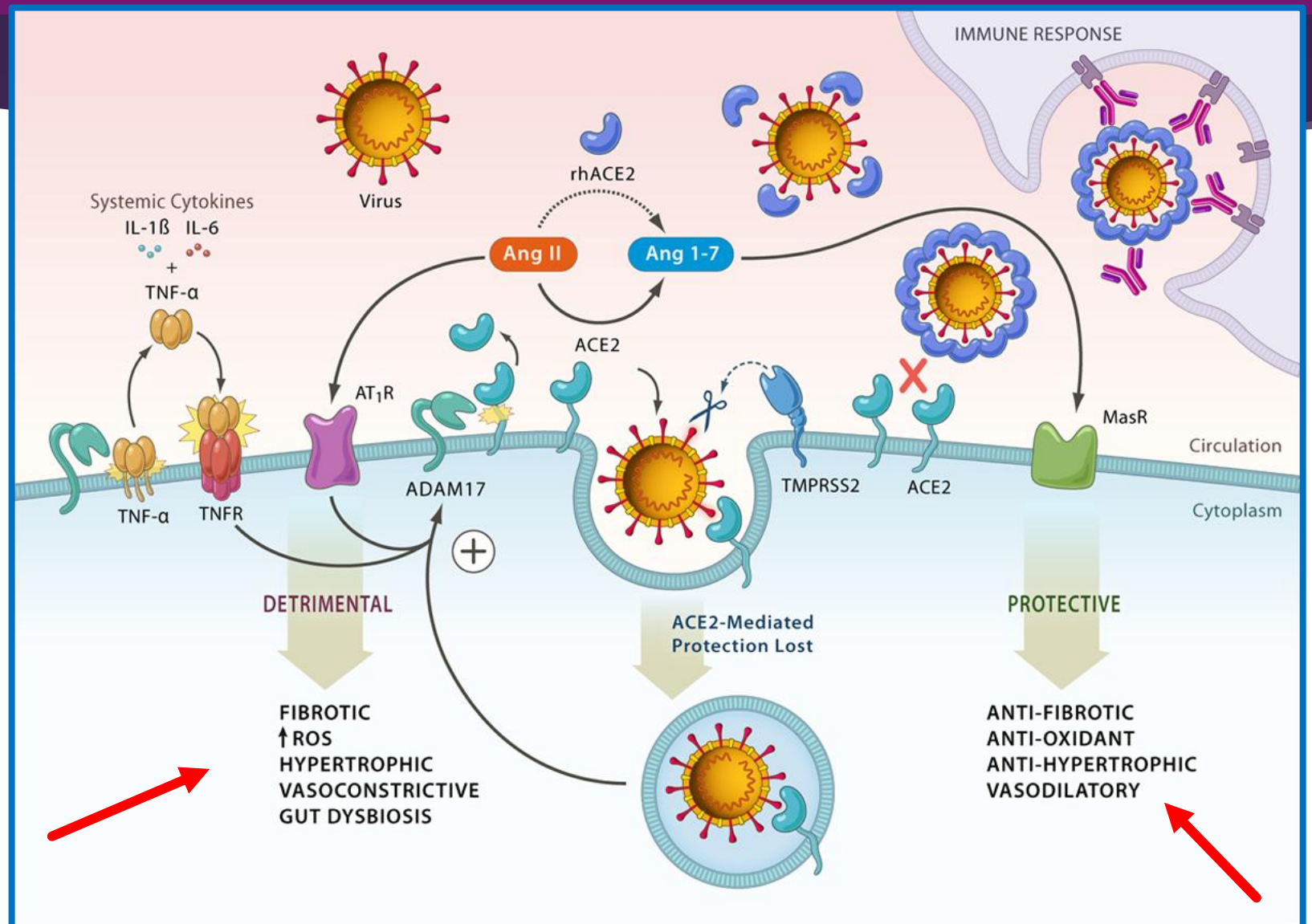
Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019 (nih.gov) and
*https://www.who.int/csr/sars/country/table2004_04_21/en

ACE2 (angiotensin-converting enzyme 2) expression throughout the body and schematic of ACE2 primary domains.



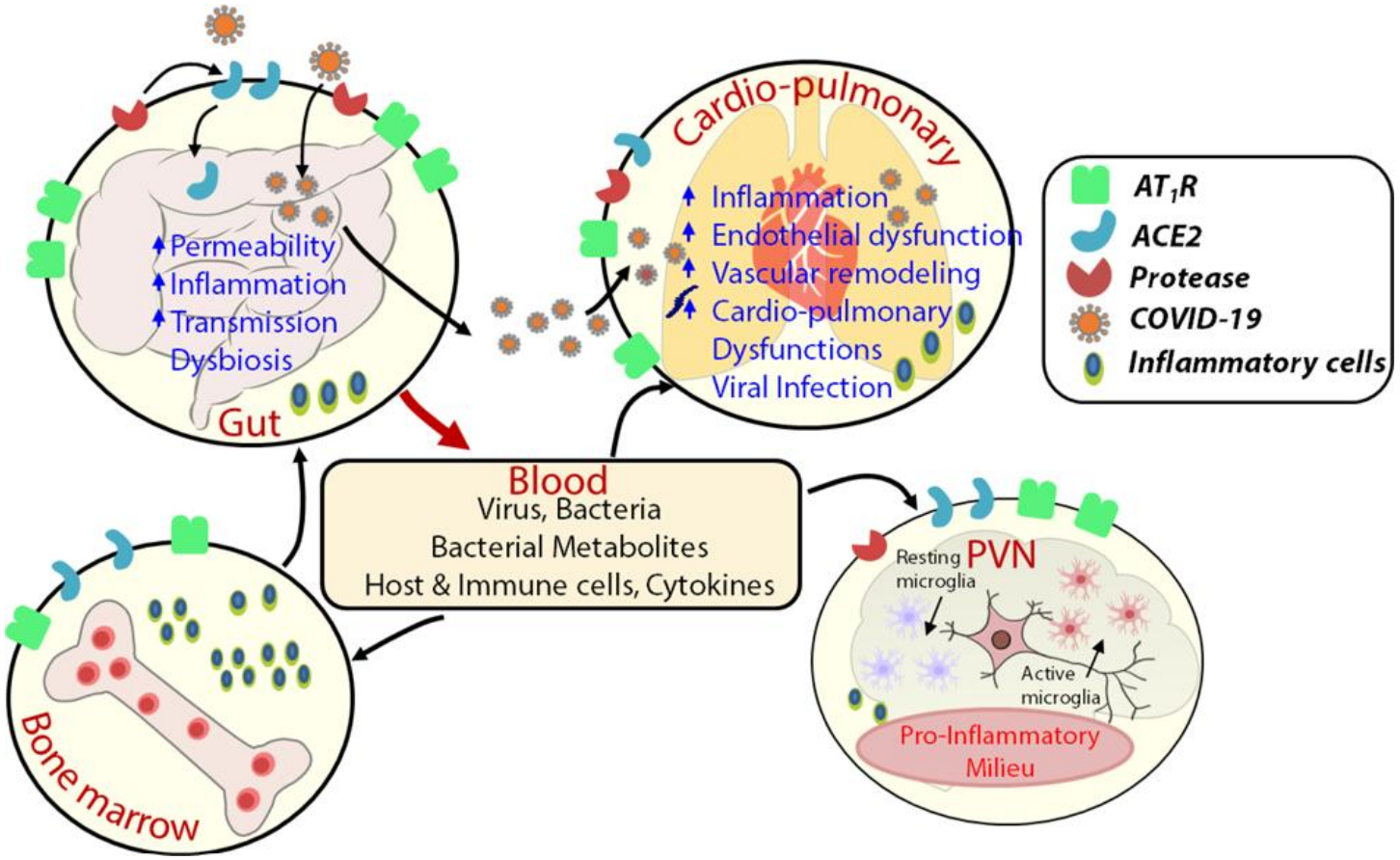
Angiotensin converting enzyme 2: a double-edged sword.*Circulation.* 2020; **142**: 426-428

Role of ACE2 (angiotensin-converting enzyme 2) in the pathogenesis of COVID-19 + the inflammatory response



Angiotensin converting enzyme 2: a double-edged sword.*Circulation.* 2020; **142**: 426-428

Link between ACE2 (angiotensin converting enzyme 2), gut dysbiosis, and cardiovascular disease.



Severe (SARS-CoV-2) enteric or pulmonary infection can further worsen the pathophysiology of the gut-lung axis through increased bacterial infiltration + inflammation in addition to worsened pulmonary function. AT1R indicates angiotensin II type 1 receptor; and COVID-19, coronavirus disease 2019.

Angiotensin converting enzyme 2: a double-edged sword.*Circulation.* 2020; **142**: 426-428

Potential Benefit of ACE Inhibitors and ATII Receptor Blockers in COVID-19

CaptoPRIL
RamiPRIL
EnalaPRIL
FosinoPRIL
LisinoPRIL
BenazePRIL
QuinaPRIL

- Azilsartan (Edarbi)
- Candesartan (Atacand)
- Eprosartan
- Irbesartan (Avapro)
- Losartan (Cozaar)

- Animal models show evidence of an attenuated lung injury by the ACE inhibitors +/or ACE receptor blockers (ARBs) from SARS-CoV infection + ventilation overdrive.
- Use of ACE inhibitors + ARBs -> lower risk of all-cause mortality among hospitalized patients.
- Prior use of ACE inhibitors/ARBs -> not associated with increased mortality or severe disease in patients with COVID-19.
- Use of ACE inhibitors in SARS-CoV-2 positive patients with hypertension is associated with ~40% lower risk of hospitalization.
- Randomized controlled studies planned -> for efficacy of ACE inhibitors + ARBs as treatment for COVID-19 (NCT04367883->2022-3, NCT04366050 ramipril done, NCT04312009 losartan in hosp. done, + NCT04311177 losartan 25 mg-completed; *https://clinicaltrials.gov*). Greater efficacy with *DD* genotype is anticipated because it is associated with higher ACE level than other genotypes should ACE gene polymorphism be tested.

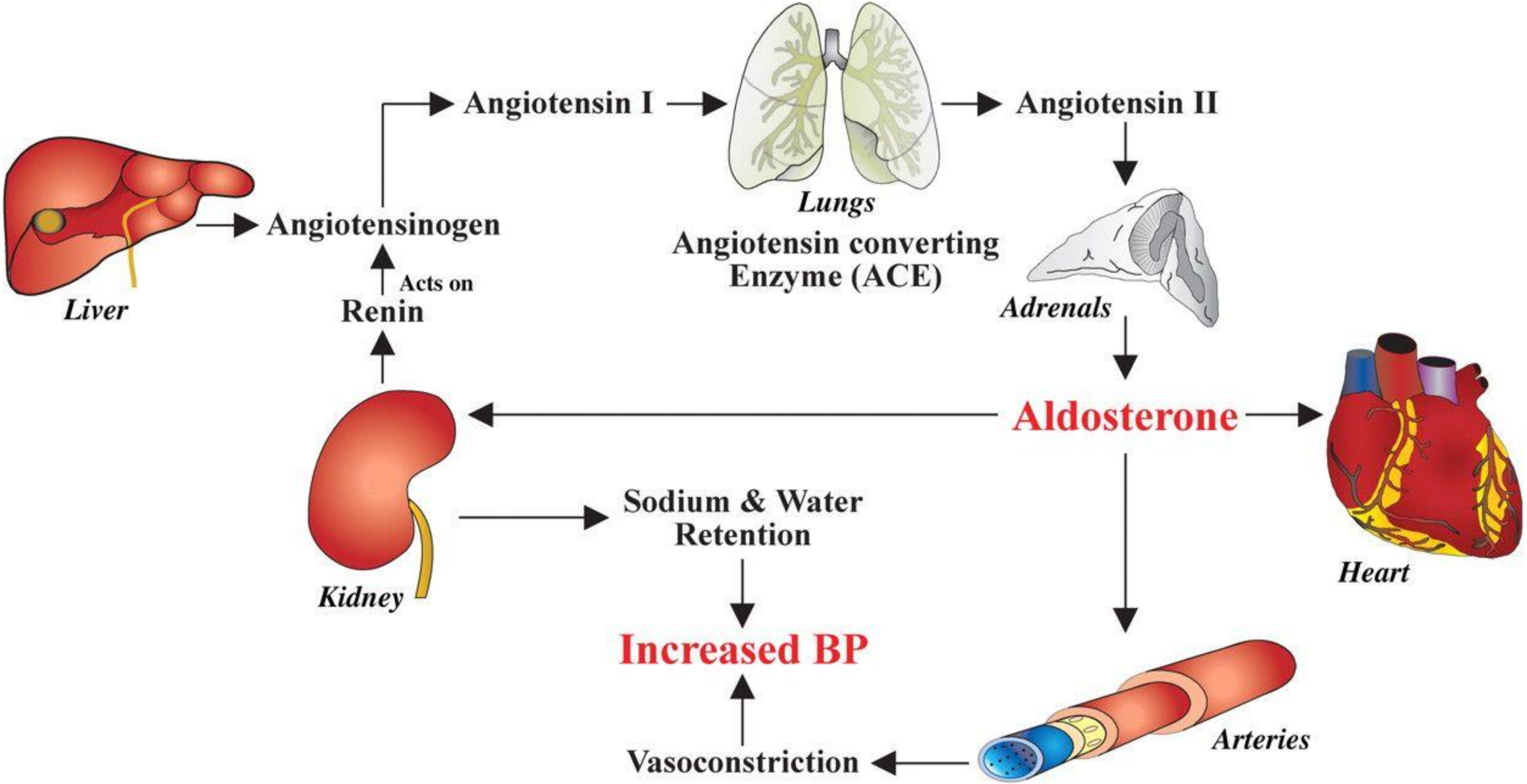
Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019 (nih.gov)

Influenza Vaccination, ACEI and ARB in the Evolution of SARS-Covid19 Infection

Evaluation of Influenza Vaccination and Treatment With ACEI and ARB in the Evolution of SARS-Covid19 Infection

Sponsors	**Lead Sponsor:** Consorci Sanitari de Terrassa **Collaborator:** Jordi Gol i Gurina Foundation Institut Català de la Salut
Source	Consorci Sanitari de Terrassa
Brief Summary	Some authors have proposed the use of the flu vaccine to reduce the severity of COVID-19 cases, while some have proposed the use of ACE Inhibitors (ACEI) or Angiotensin Receptor blockers (ARB), since this virus shares hemagglutinin as a transmission mechanism and acts on the ACE2 enzyme during infection. The aim is to evaluate whether the admitted patients who are previously vaccinated or those who were already receiving treatment show a better evolution.

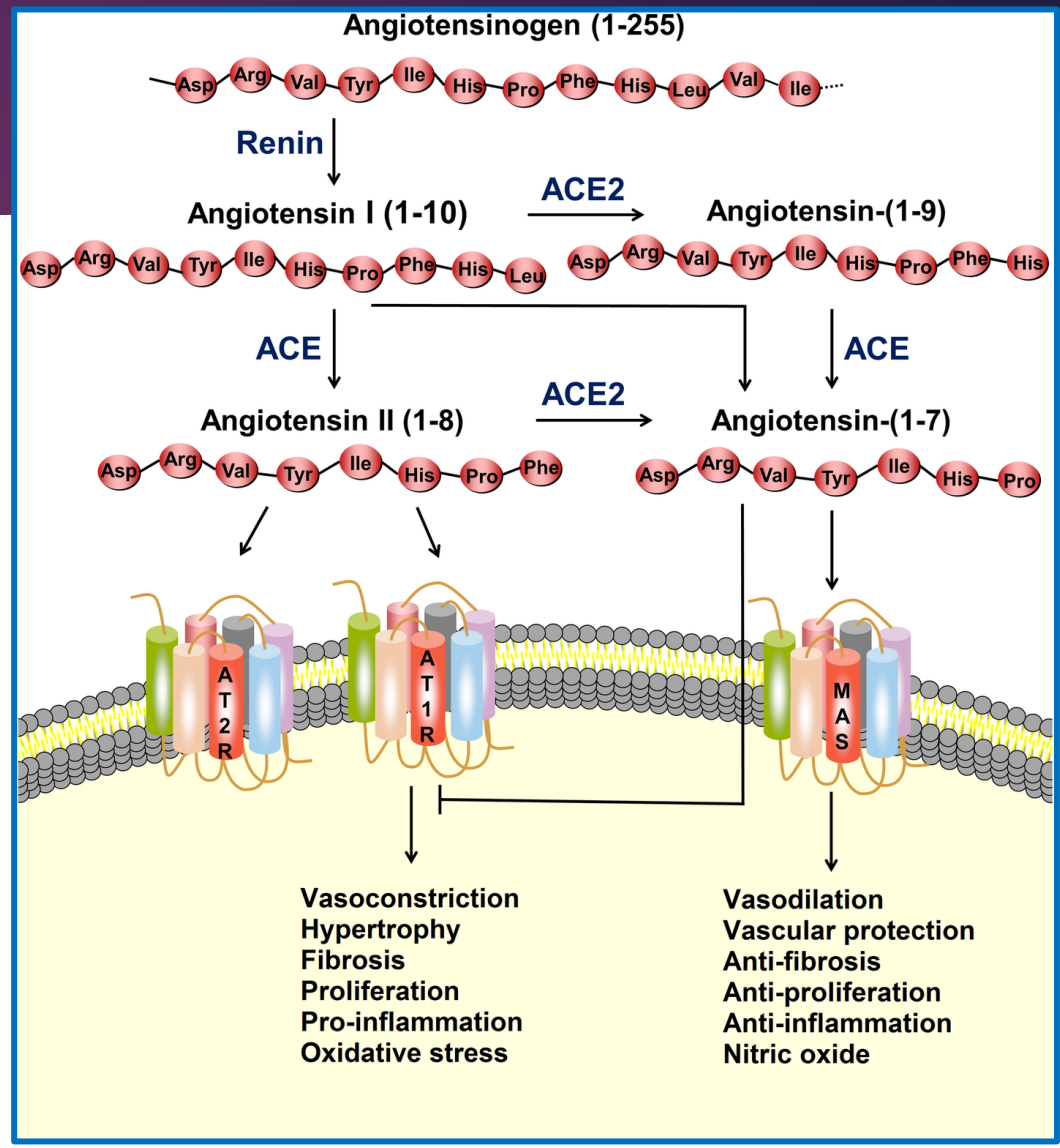
https://ichgcp.net/clinical-trials-registry/NCT04367883


Angiotensin I
Angiotensin II
Lungs
Angiotensin converting
Enzyme (ACE)
Liver
Angiotensinogen
Acts on
Renin
Adrenals
Aldosterone
Heart
Kidney
Sodium & Water
Retention
Increased BP
Vasoconstriction
Arteries

The renin-angiotensin system (RAS) and ACE2/angiotensin-(1–7)/MAS axis

- The protease renin converts angiotensinogen to Ang-I, which is subsequently converted to Ang-II by angiotensin-converting enzyme (ACE).
- Ang-II can bind to the angiotensin type 1 receptor (AT1R) to exert actions, such as vasoconstriction, hypertrophy, fibrosis, proliferation, inflammation, and oxidative stress.
- ACE2 can covert Ang-I and Ang-II to angiotensin-(1–7). Angiotensin-(1–7) binds to the MAS receptor to exert actions of vasodilation, vascular protection, anti-fibrosis, anti-proliferation, and anti-inflammation.
- Ang-II can also bind to the angiotensin type 2 receptor (AT2R) to counteract the aforementioned effects mediated by AT1R

Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19



Renin-Angiotensin-Aldosterone system (RAAS) plays an important role in the pathogenesis of COVID-19

- Angiotensin-converting enzyme (ACE or ACE1) catalyzes the synthesis of Angiotensin-II (Ang-II) from Ang-I, and ACE2 hydrolyzes Ang-II into Ang-1–7. Ang-II binds to the AT1-receptor driving vasoconstriction, fibrosis, inflammation, thrombosis, among other responses; while Ang-1–7 binds to the AT2-receptor with increased vasodilation and reduced fibrosis, inflammation, and thrombosis.
- ACE + ACE2 are seen as opposite players in the balance that determines the risk of developing hypertension and cardiovascular disease.
- In the lung, ACE2 drives a protective response by reducing edema, permeability and pulmonary damage.
- Hypertension and cardiovascular disease are frequent comorbidities in COVID-19, + strongly associated with risk of hospitalization + death in individuals exposed to SARS-CoV-2.

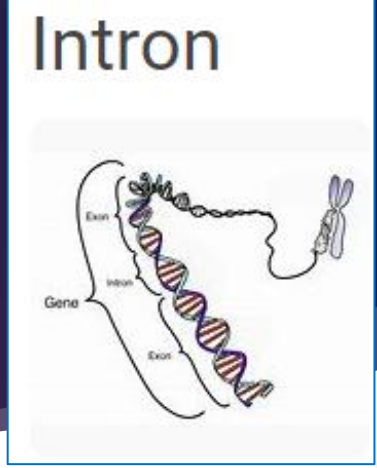
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456966/#s0040title

Renin-Angiotensin-Aldosterone system (RAAS) plays an important role in the pathogenesis of COVID-19

- Acquired + inherited factors associated with differences in expression + function of RAAS components explain the risk of developing COVID-19 + adverse events.
- ACE2 expression in lungs markedly decreases with age + is greater in men than in women.
- Higher risk for adverse outcomes in elderly and male.
- Conditions related to reduced ACE2 expression increase the risk for hypertension, cardiac hypertrophy, + heart failure.
- High activity of ACE would incr. risk of lung + cardiovascular disease by increased activity of Ang-II/AT1R axis.
- Common variants of 2 *ACE* genes are associated with risk of HTN, heart disease, renal failure, + pulmonary disease.
- *ACE* insertion/deletion (I/D) is one of the best characterized human polymorphisms.
- Peoples with D/D genotype showed highest blood ACE levels, + would explain the higher risk for cardiovascular + respiratory disease among those who are deletion-homozygous. This polymorphism has been related to outcome in acute respiratory distress syndrome (ARDS), + with progression of pneumonia in SARS.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456966/#s0040title

Renin-Angiotensin-Aldosterone system (RAAS) plays an important role in the pathogenesis of COVID-19



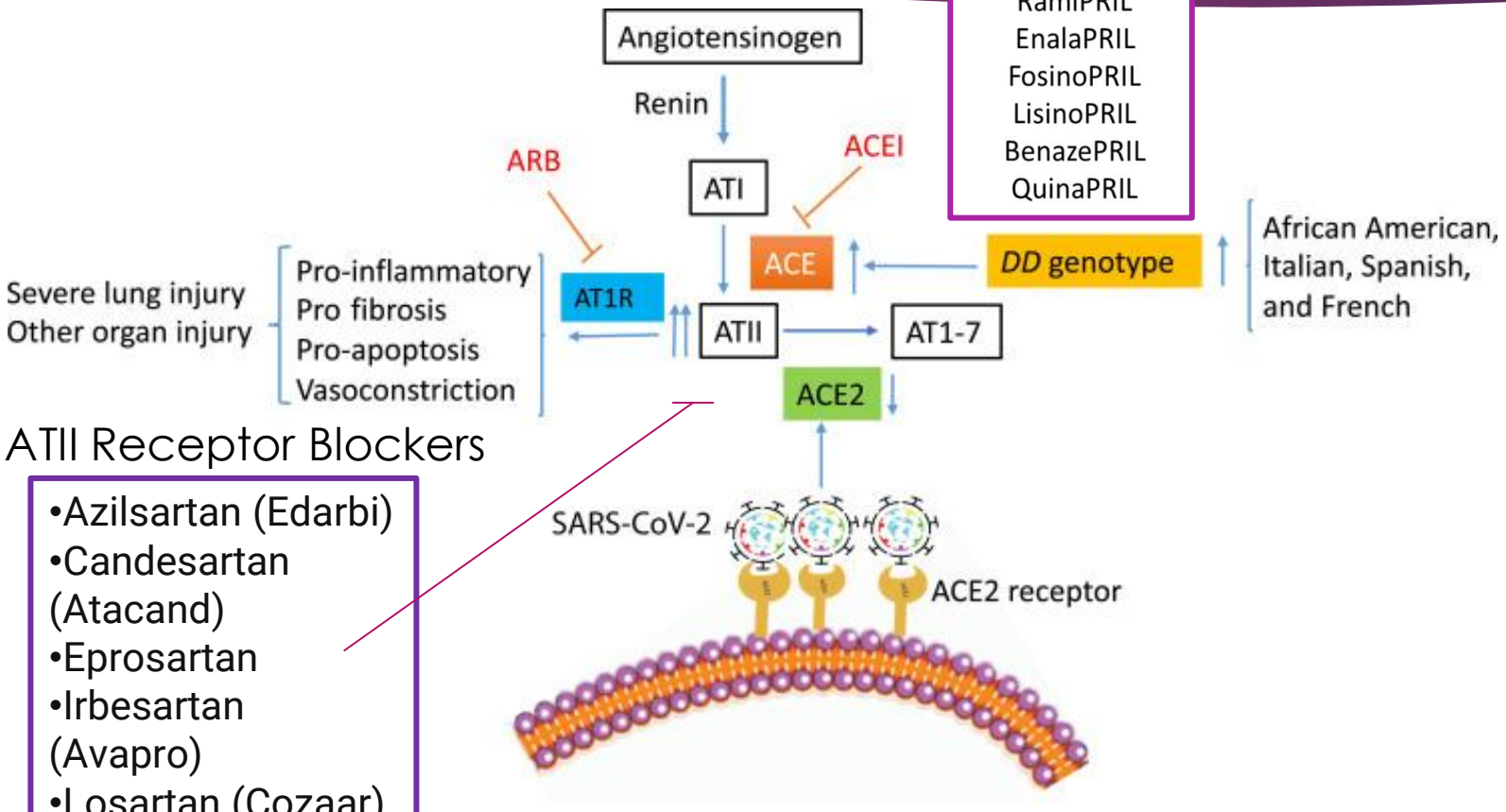
- *ACE2* gene is on chromosome X + several single nucleotide polymorphisms (SNPs) have been investigated as risk factors for hypertension and heart failure, including a G to A change at nucleotide + 4 of intron 3 (SNP rs2285666).
- *ACE2* is on chromosome X has been seen as a disadvantage for male carriers of alleles linked to a lower ACE2 expression + higher prevalence of severe COVID-19 in males.
- SARS-CoV down-regulates myocardial ACE2 expression +explains myocardial inflammation, damage and adverse cardiac outcomes in patients with SARS.
- A role for ACE/ACE2 imbalance in the pathogenesis of COVID-19. Variants of these genes associated with differences in gene expression and protein function might explain the individual's predisposition to manifest the disease symptoms + risk for hospitalization + adverse events.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456966/#s0040title

Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019

ACE Inhibitors

- CaptoPRIL
- RamiPRIL
- EnalaPRIL
- FosinoPRIL
- LisinoPRIL
- BenazePRIL
- QuinaPRIL



ATII Receptor Blockers

- Azilsartan (Edarbi)
- Candesartan (Atacand)
- Eprosartan
- Irbesartan (Avapro)
- Losartan (Cozaar)

Illustration of the impact severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has on the main metabolic pathways driven by angiotensin-converting enzyme (ACE) and ACE2 in the renin-angiotensin system, proposed mechanisms of ACE *DD* genotype in the severe lung injury of coronavirus disease 2019, and the potential impact of ACE *DD* genotype in the high-risk population. The potential therapeutic targets for ACE inhibitors (ACEIs) and angiotensin (AT) 1 receptor blockers (ARBs) are also shown.

Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019 (nih.gov)

Potential Benefit of ACE Inhibitors and ATII Receptor Blockers in COVID-19-

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- Losartan (Cozaar)

Summary

- ACE2 is a binding receptor for SARS-CoV-2 to enter the cell.
- Down-regulation of ACE2 as a result of SARS-CoV-2 infection is likely the important mechanism of acute lung injury or ARDS related to COVID-19 because of the resultant imbalance between ACE and ACE2 and the overproduction of ATII.
- ACE gene polymorphism, which accounts for the differences of the ACE level in general population, may be responsible for the susceptibility to severe lung injury in COVID-19 patients. Absence of ACE *D/D* genotype in patients with COVID-19 may be **protective** against developing severe lung injury.
- Conversely, presence of ACE *D/D* allele may be favorable for ACE inhibitors and ARB therapy.
- It is desirable to test ACE gene polymorphism for COVID-19 patients in the ongoing clinical trials with ACE inhibitors and ARBs.

Angiotensin-Converting Enzyme Gene Polymorphism and Severe Lung Injury in Patients with Coronavirus Disease 2019 (nih.gov)

ACE gene variants raise risk of severe COVID-19 in patients with hypertension, dyslipidemia or diabetes. A pilot study (SPAIN)

- **rs4341 + rs4343** polymorphisms of the angiotensin converting enzyme (ACE) gene, key regulator of the renin-aldosterone-angiotensin system (RAAS), helps explain different outcomes of 128 COVID-19 patients with diverse degree of severity (33 asymptomatic or mildly asymptomatic, 66 hospitalized in the general ward, and 29 admitted to the ICU).
- G allele of rs4341 and rs4343 was associated with severe COVID-19 in hypertensive patients, independently of gender ($p < 0.05$) and higher severity of COVID-19 in dyslipidemic ($p < 0.01$).
- Study suggests G-containing genotypes of rs4341 and rs4343 confer an additional risk of adverse COVID-19 prognosis.
- rs4341 + rs4343 polymorphisms of ACE could be predictive markers of severity of COVID-19 in those patients with hypertension, dyslipidemia or diabetes.
- Knowledge of genetic data could contribute to precision management of SARS-CoV-2 infected patients when admitted to hospital.

https://www.medrxiv.org/content/10.1101/2021.03.24.21253576v1.full.pdf)

THANK YOU!

IVERMECTIN FOR COVID-19

61 TRIALS, 578 SCIENTISTS, 19,432 PATIENTS

32 RANDOMIZED CONTROLLED TRIALS

85% IMPROVEMENT IN 14 PROPHYLAXIS TRIALS RR 0.15 [0.09-0.25]

74% IMPROVEMENT IN 26 EARLY TREATMENT TRIALS RR 0.26 [0.16-0.43]

46% IMPROVEMENT IN 21 LATE TREATMENT TRIALS RR 0.54 [0.41-0.71]

68% IMPROVEMENT IN 23 MORTALITY RESULTS RR 0.32 [0.21-0.50]

62% IMPROVEMENT IN 32 RANDOMIZED CONTROLLED TRIALS RR 0.38 [0.27-0.53]

SUMMARY OF RESULTS REPORTED IN IVERMECTIN TRIALS FOR COVID-19. 07/04/21. IVMMETA.COM

5 mechanisms of actions-> works on all the variants