Susceptibility and severity of COVID -19

Prof. Vandana Rai

Department of Biotechnology VBS Purvanchal University, Jaunpur

COVID-19

- Severe acute respiratory syndrome coronavirus- 2 (SARS-CoV-2) causes coronavirus disease 19 (COVID-19)
- Size -100nm(0.1um)
- Global pandemic (March 11,2020 WHO).
- SARS-CoV-2 is highly contagious and the present fatality rate of COVID 19 is approximately 1.89% in India.
- SARS COV-2 is an enveloped virus and contains` 29 Kb plus stranded RNA genome(14 ORFs, 29 genes).
- Nonstrucutral proteins-16, Structural protein-4, accessory proteins-9
- COV-2 uses human angiotensin converting enzyme (ACE2) as receptor for the entry in the cell.



Novel Coronavirus SARS-CoV-2

Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID

<u>https://www.flickr.com/photos/niaid/49641177821/in/album-</u> 72157712914621487



Alanagreh et al. 2020.Pathogen, 9,331

SARS-CoV-2 binds to the ACE2 receptor after activation of the spike protein by TMPRSS2

- **Step 1**: binding of the N-terminal portion of the viral protein unit S1 to a pocket of the ACE2 receptor.
- **Step 2:** protein cleavage between the S1 and S2 units, which is operated by the receptor transmembrane protease serine 2 (TMPRSS2), a member of the TMPRSS subfamily.

• **Step 3**: after S1 detachment, the remaining viral S2 unit undergoes a conformational rearrangement which drives and completes the fusion between the viral and cellular membrane, with subsequent entry of the virus into cell.



Mousavizadeh and Ghasemi, 2020





https://en.wikipedia.org/wiki/Angiotensin-converting_enzyme

Angiotensin II is a potent vasoconstrictor in a substrate concentration-dependent manner.

Angiotensin II binds to the type 1 angiotensin II receptor(AT1), which sets off a number of actions that result in vasoconstriction and therefore increased blood pressure.



Renin-anglotensin-aldosterone system

https://en.wikipedia.org/wiki/Angiotensin-converting_enzyme

Risk Factors

- Old age (>65 years) (Immunosenescence)
- Obesity (increase ACE2 expression)
- Smoking (increase ACE2 expression)
- Gender (Testosterone driven COVID19 theory)

People who have underlying medical conditions such as

- Cardiovascular Diseases (dysregulated renin angiotensin system (RAS),
- **Respiratory Diseases**
- Diabetes (dysregulated renin angiotensin system (RAS)
- along with immunodeficiency

COVID-19 infection and Renin Angiotensin System (RAS)





Gheblawi et al.,2020

- Numerous studies reported and concluded that severe COVID 19 disease is determined by both genetic and acquired risk factors.
- In case of SARS-CoV-2 infection, genetics of host may play a role through polymorphisms of genes which encode for
- i. host proteins that are exploited by SARS-CoV-2 for entry to the host cell (ACE2 receptor and TMPRSS2 protease), or
- ii. immune response proteins which provide protection against the virus like cytokines.

Genetic association studies are currently ongoing to unravel such hypotheses, and have found correlations between ACE2 variants and COVID-19 susceptibility.

ACE 2 gene

SARSCoV-2 exploits angiotensin converting enzyme 2 (ACE2) for its entrance inside the cells, this gene is a putative risk factor for this infection.



- ACE2 maps to chromosome Xp22, spans 39.98 kb of genomic DNA, and contains 20 introns and 18 exons.
- Some structural variations of human ACE2 have been identified that are characterized by a lower binding affinity with the spike viral protein, with potential protective implications.

SNP and ACE 2 Gene

- More than 200 single nucleotide polymorphisms (SNP) are reported in ACE 2 gene, out of which
- S19P,
- I21V,
- E23K,
- K26R,
- T27A,
- N64K,
- **T92**I,
- **Q102P** and
- **H378R** variants are predicted to increase COVID 19 susceptibility.



Angiotensin- converting enzyme ACE 1 gene

ACE 1 gene is localised on band 17q23 and spans approximately 21 kb DNA.

The ACE gene consisting of 26 exons and 25 introns.

The I/D polymorphism (rs1799752) affects intron 16.

The ACE1 D gene is associated with low levels of expression of the ACE2 gene.



Agarose gel picture showing Genomic DNA

Agarose gel picture showing I and D amplicons

Transmembrane protease serine 2

- TMPRSS2 activity is essential for viral spread and pathogenesis in the infected host.
- TMPRSS2 gene is located on chromosome 21.
- Variant rs35074065 is associated with high expression of TMPRSS2 but with a low expression of the interferon (IFN)α/β-inducible gene.
- Individuas, who carried single nucleotide polymorphisms associated with higher TMPRSS2 expression (rs2070788 and rs383510) may be more susceptible to SARS CoV2.





Irham et al., Biochemical and Biophysical Research Communications 529 (2020) 263e.

• Personalized genetic approach may be used as an indicator for the assessment of host specific outcome of the severity of the COVID 19 disease.