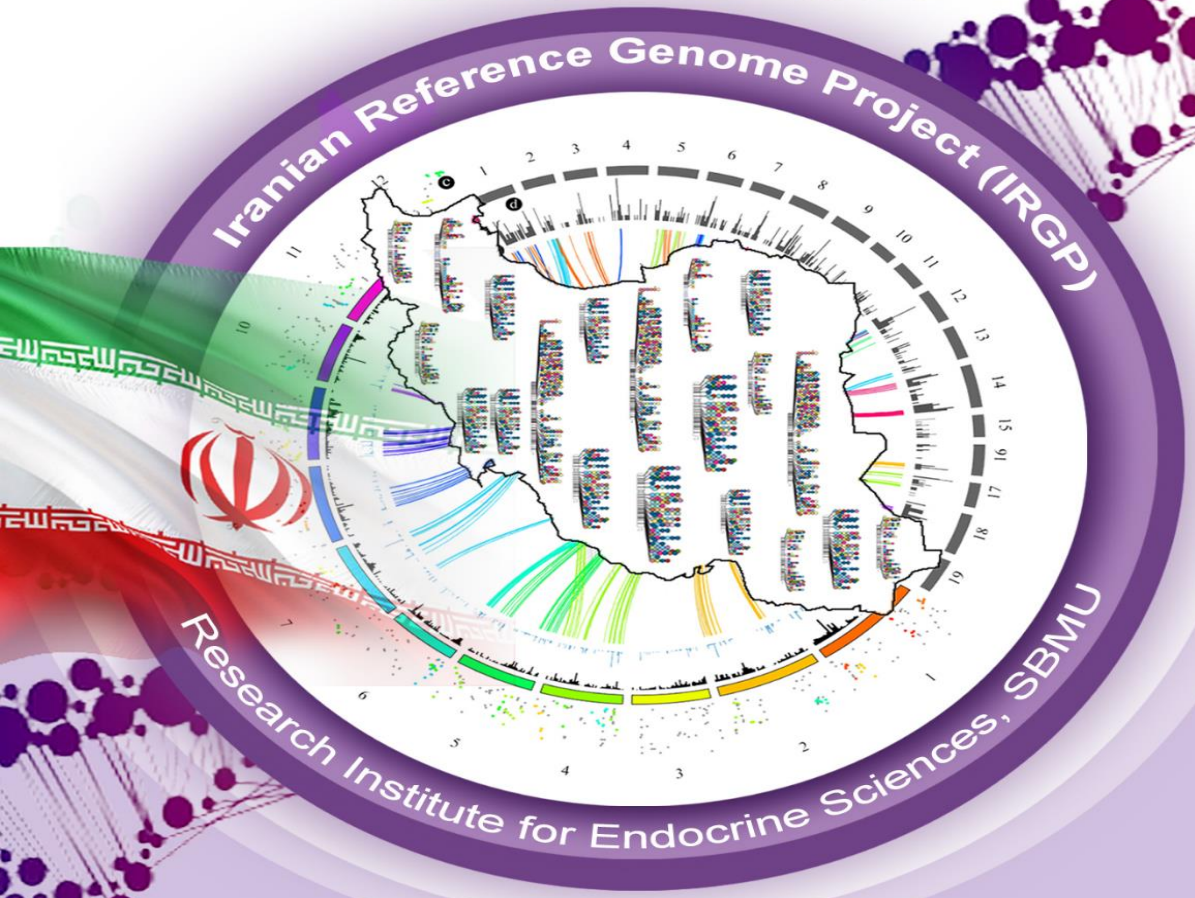

بسم الله الرحمن الرحیم

ژمیران

ژنوم مرجع ایرانیان



Molecular markers associated with the COVID-19 susceptibility

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Overview

1. What are genetic markers?

2. Why the genetic markers are important for the COVID-19?

3. Are the genetic markers related to susceptibility to the COVID-19?

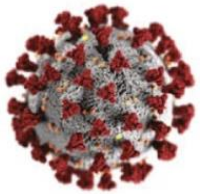
Demographic and biological variables may characterize the high-risk patients

Race

Sex

Genetics

Blood group



Viral genotype

Age

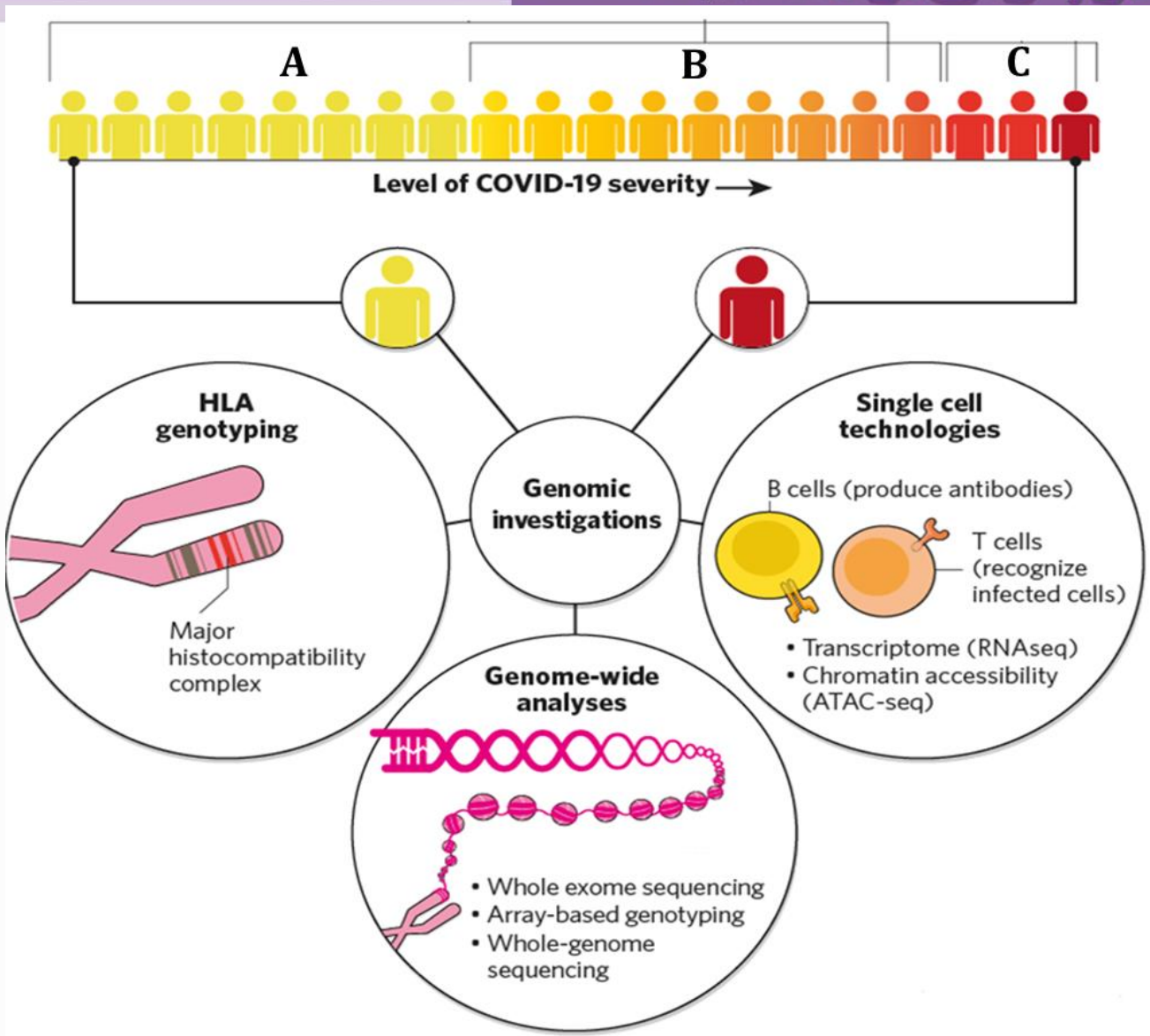
Cardiovascular and metabolic diseases

Genetic Markers

Genetic markers are detectable variations of DNA /RNA sequence with known chromosome locations.

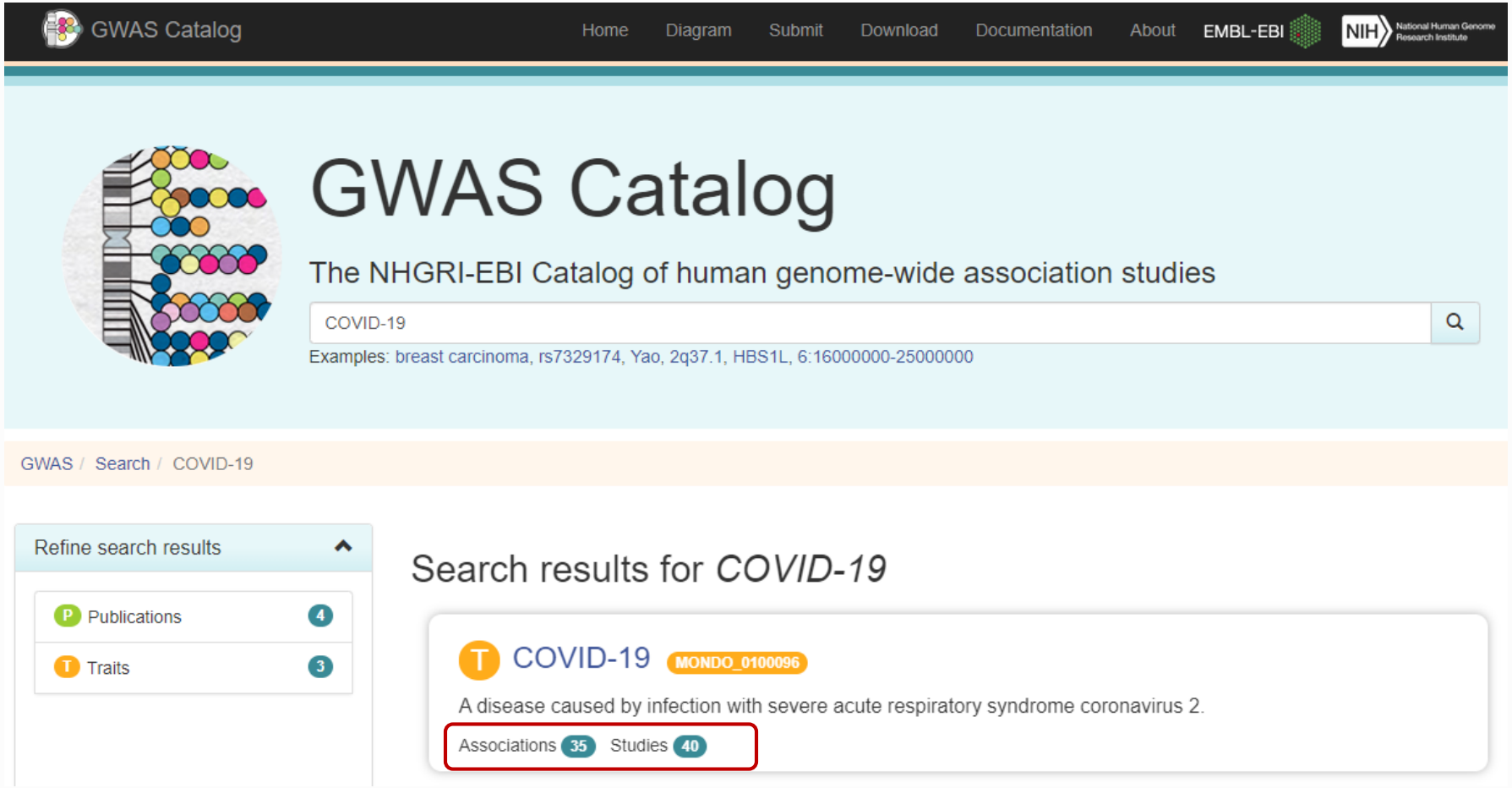
- Single Nucleotide Polymorphism (SNP)
- Insertion/Deletion of multiple nucleotides (Indel)
- Structural variations (SV)
- Gene transcript level (expression), gene may be coding or non-coding.

Genetic background might determine the inter-individual differences associated with COVID-19



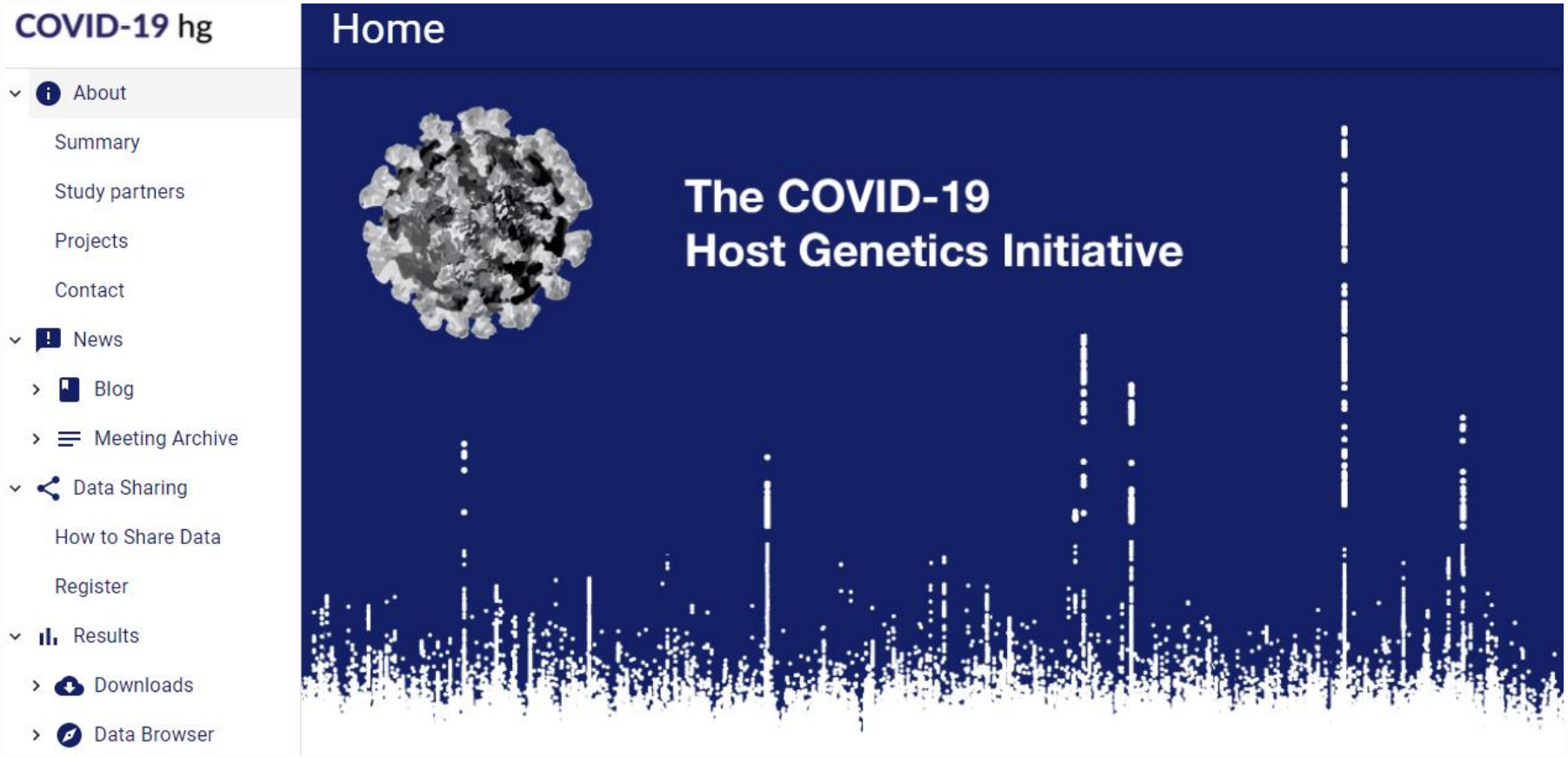
GWAS Catalog

Until now, 40 COVID-19 Genome-Wide Association Studies (GWAS) are recorded in the GWAS catalog database.

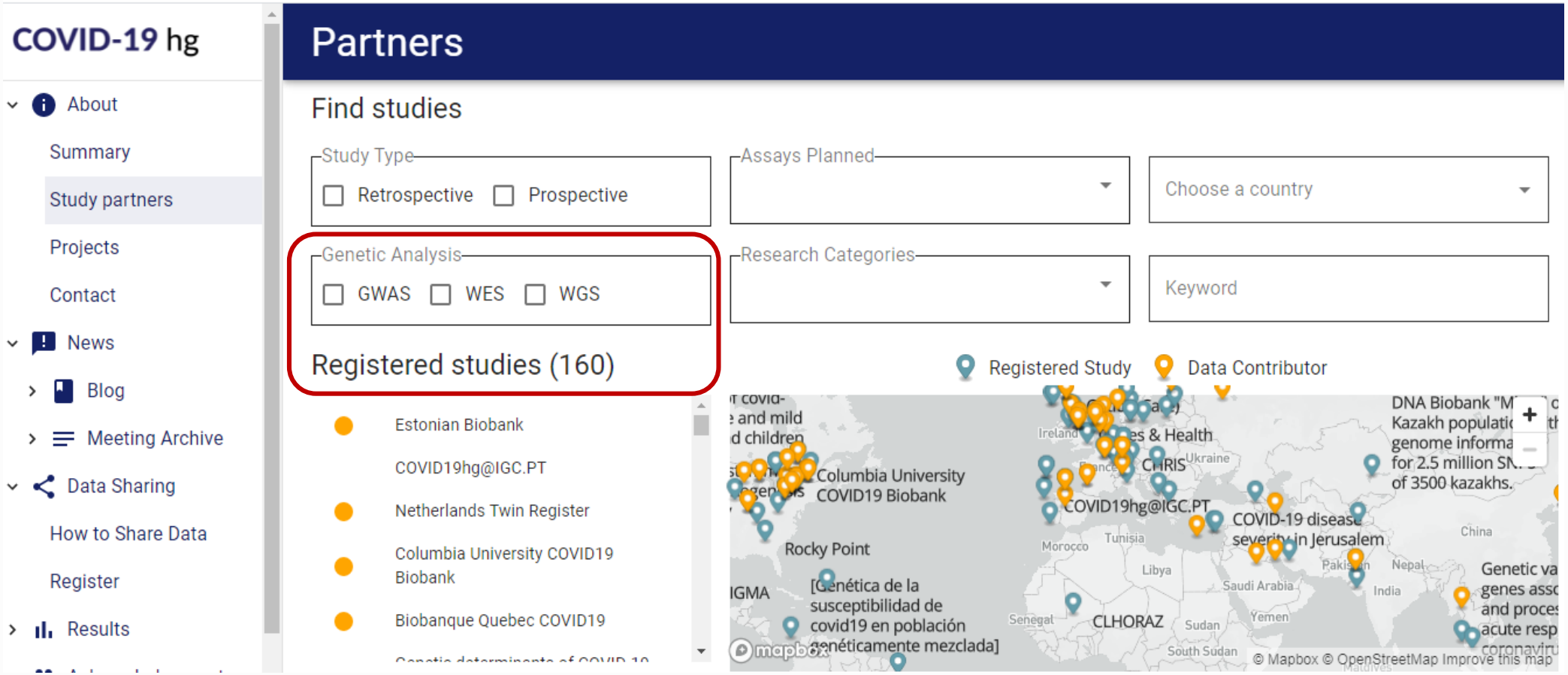


The COVID-19 host genetics initiative

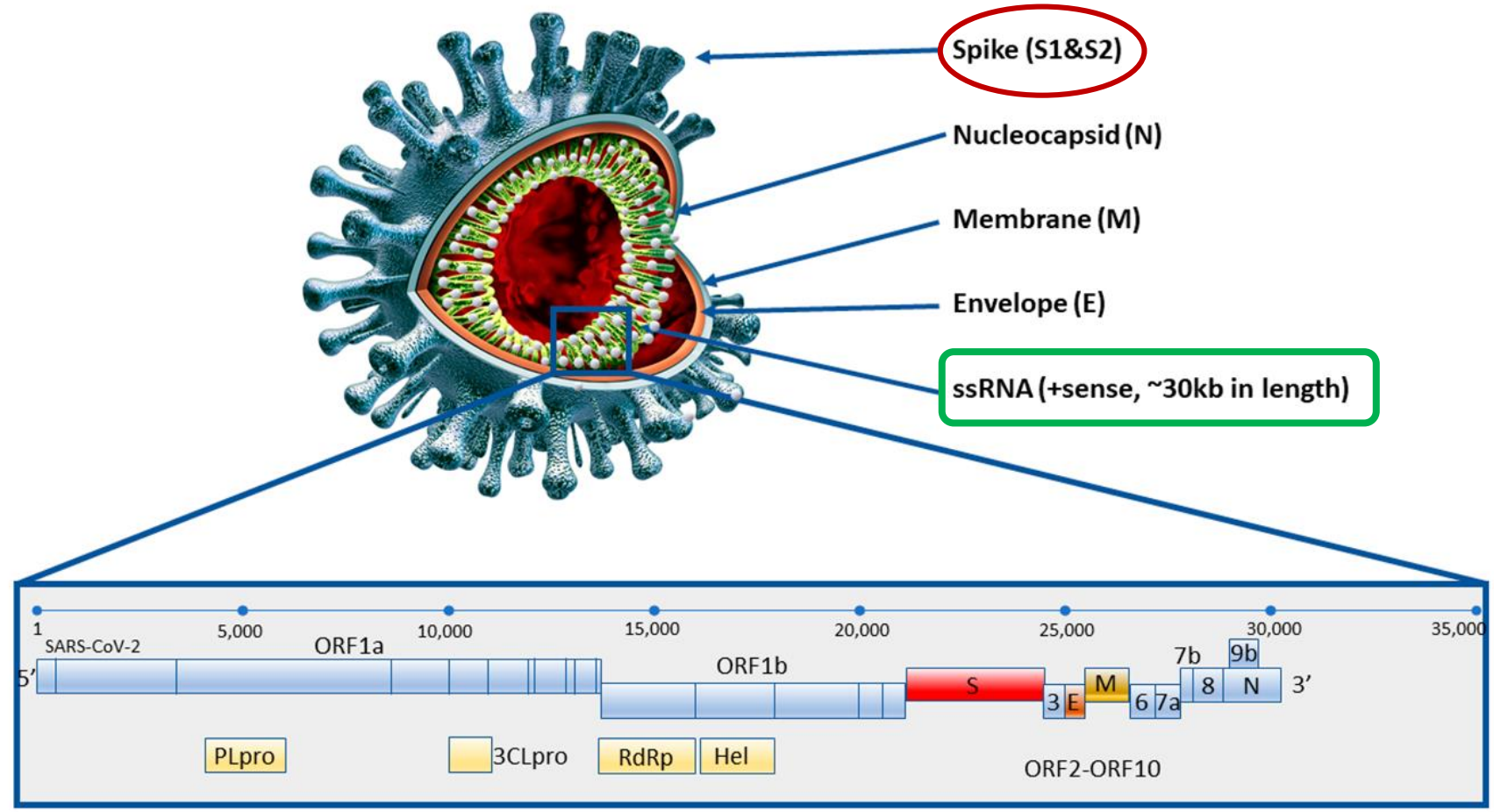
The COVID-19 host genetics initiative brings together the human genetics community to generate, share, and analyze data to learn the genetic determinants of COVID-19 susceptibility and severity.



160 genetic studies registered in the COVID-19 host genetics initiative database



SARS-CoV-2 structure

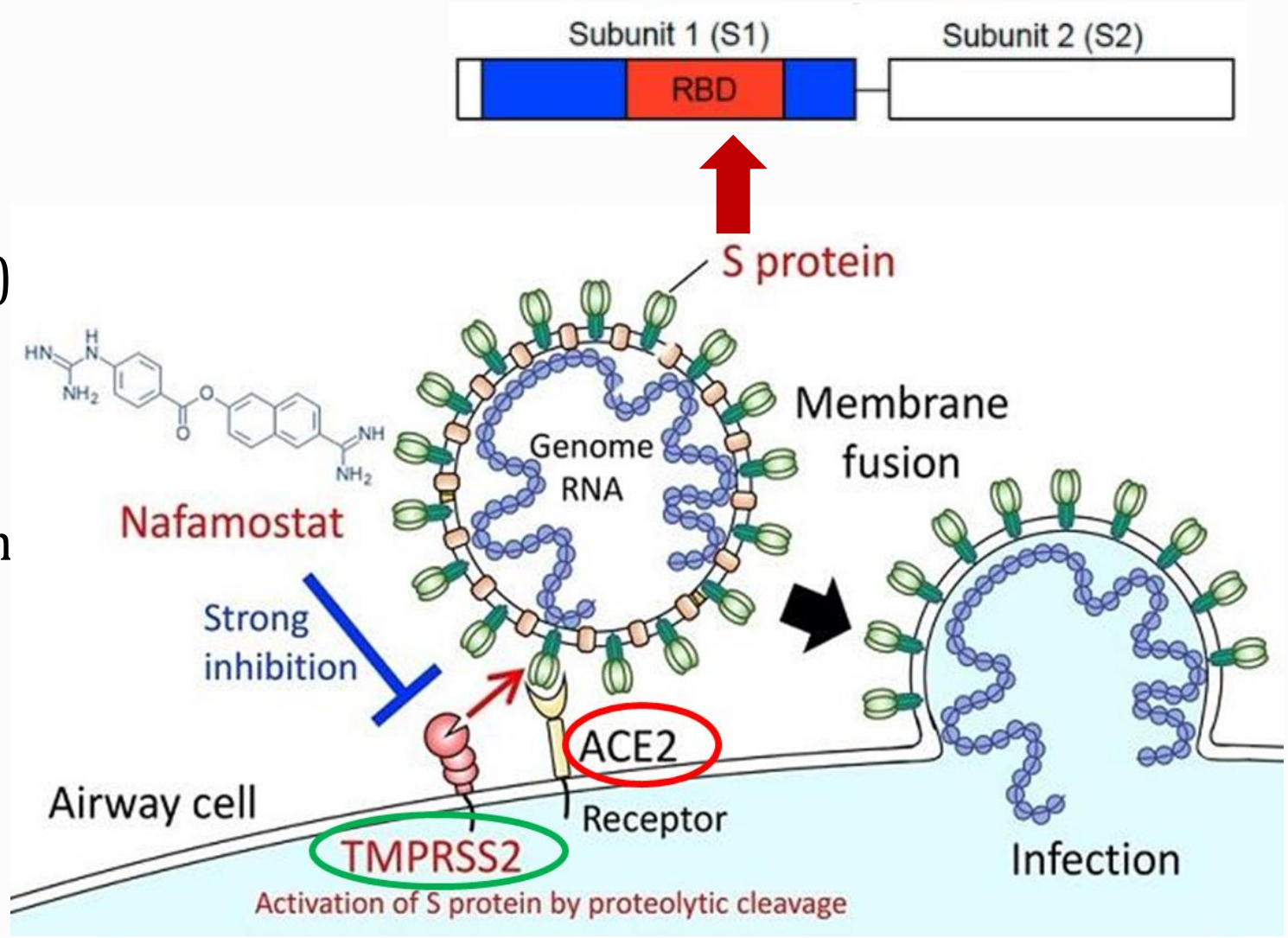


Non-structural proteins (NSP)

Structural proteins

Cell entry of SARS-CoV-2

Cell entry mechanism of SARS-CoV-2 involves a cell surface receptor (ACE2) to bind and spike protein priming by cellular proteases, which facilitates membrane fusion. TMPRSS2 was the first protease that was associated with the S protein priming.



Our first study

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SARS-CoV-2 infection susceptibility influenced by *ACE2* genetic polymorphisms: insights from Tehran Cardio-Metabolic Genetic Study

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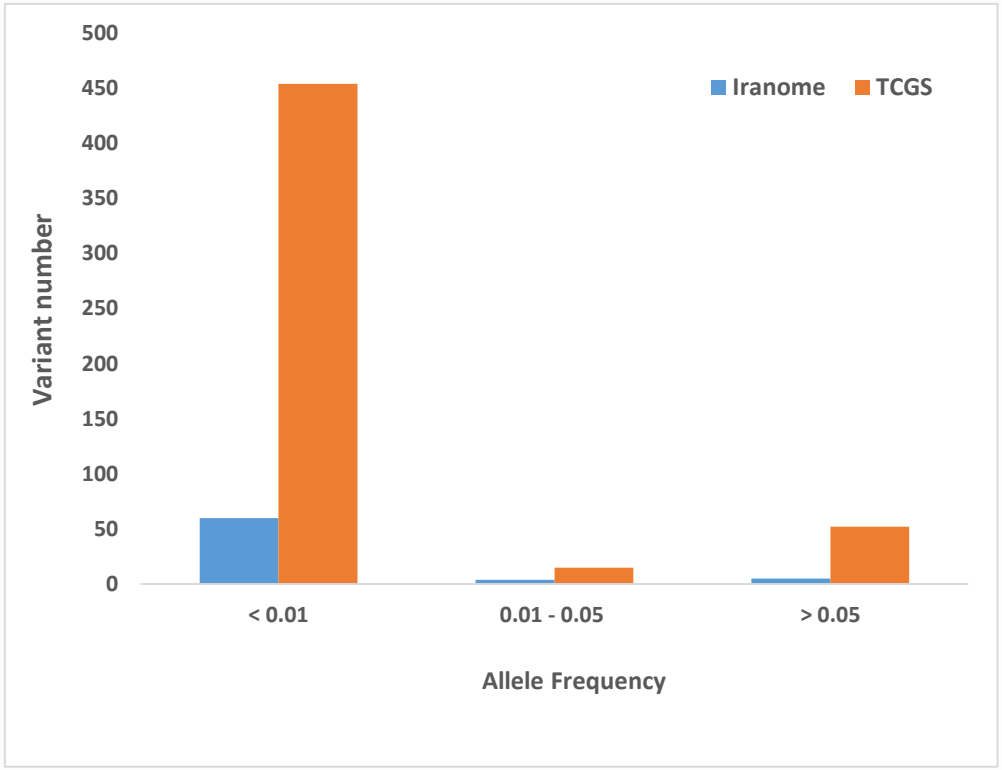
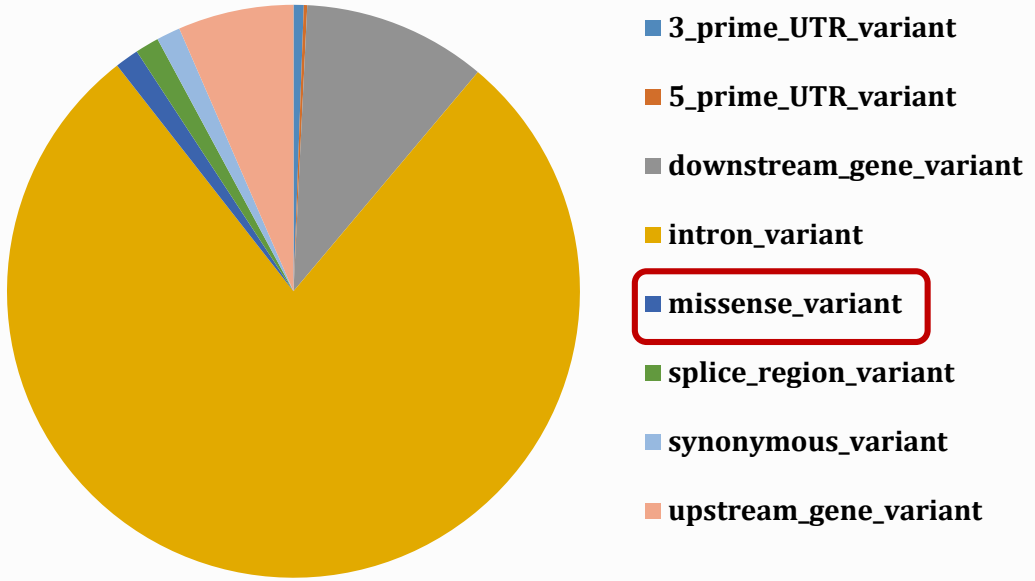
The genetic variations among individuals are one of the notable factors determining disease severity and drug response. Nowadays, COVID-19 pandemic has been adversely affecting many aspects of human life. We used the Tehran Cardio-Metabolic Genetic Study (TCGS) data that is an ongoing genetic study including the whole-genome sequencing of 1200 individuals and chip genotyping of more than 15,000 participants. Here, the effect of *ACE2* variations by focusing on the receptor-binding site of SARS-CoV-2 and ACE2 cleavage by TMPRSS2 protease were investigated through simulations study. After analyzing TCGS data, 570 genetic variations on the *ACE2* gene, including single nucleotide polymorphisms (SNP) and insertion/deletion (INDEL) were detected. Interestingly, two observed missense variants, K26R and S331F, which only the first one was previously reported, can reduce the receptor affinity for the viral Spike protein. Moreover, our bioinformatics simulation of 3D structures and docking of proteins explains important details of ACE2-Spike and ACE2-TMPRSS2 interactions, especially the critical role of Arg652 of ACE2 for protease function of TMPRSS2 was uncovered. As our results show that the genetic variation of *ACE2* can at least influence the affinity of this receptor to its partners, we need to consider the genetic variations on *ACE2* as well as other genes in the pathways that contribute to the pathogenesis of COVID-19 for designing efficient drugs and vaccines.

ACE2 variations within the Iranian population

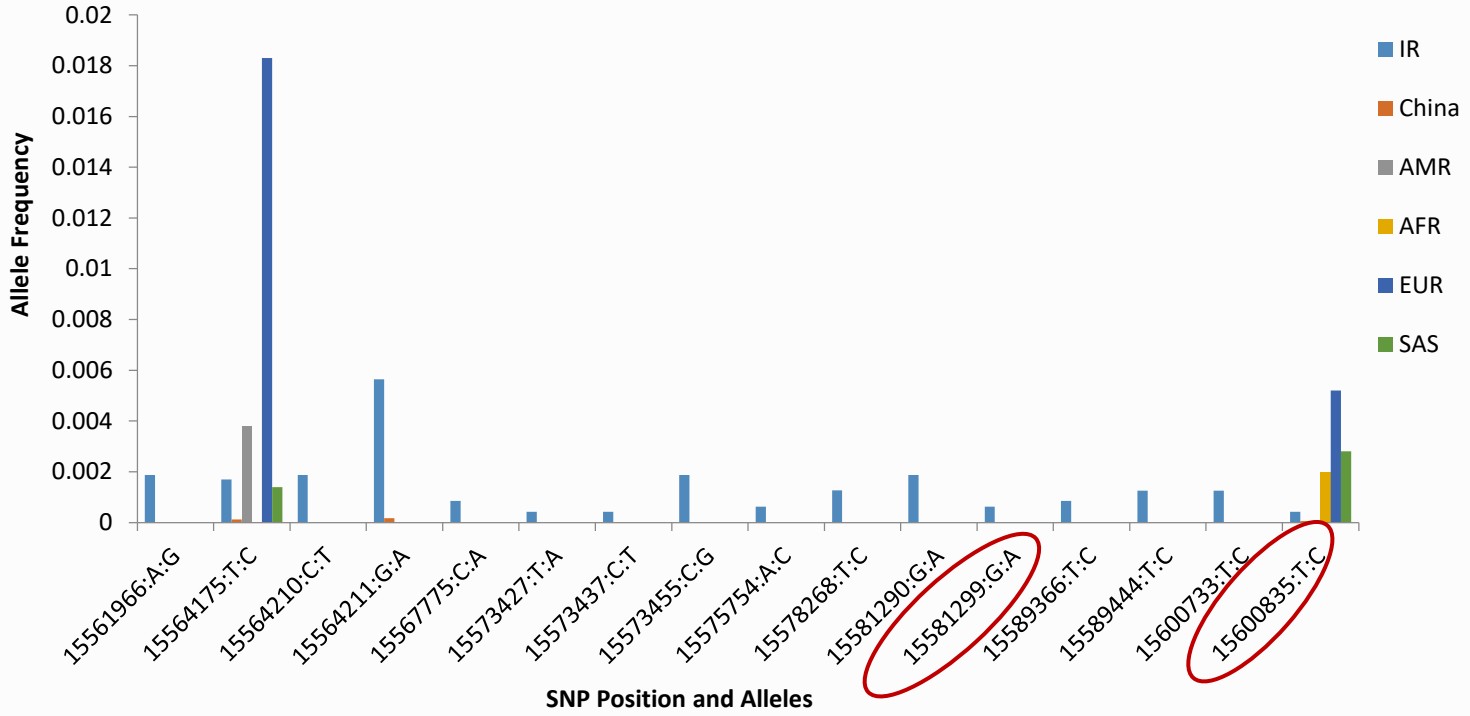




570 variations were found in the Iranian population (TCGS and Iranome)

Missense *ACE2* variants in Iran, China, and 1000 Genome Project populations

K26R (15600835:T:C) and **S331F** (15581299:G:A), which later was identified only in the Iranian population, can reduce the receptor affinity for the viral spike protein through increasing the binding free energy.



eQTL variants affect the *ACE2* expression levels

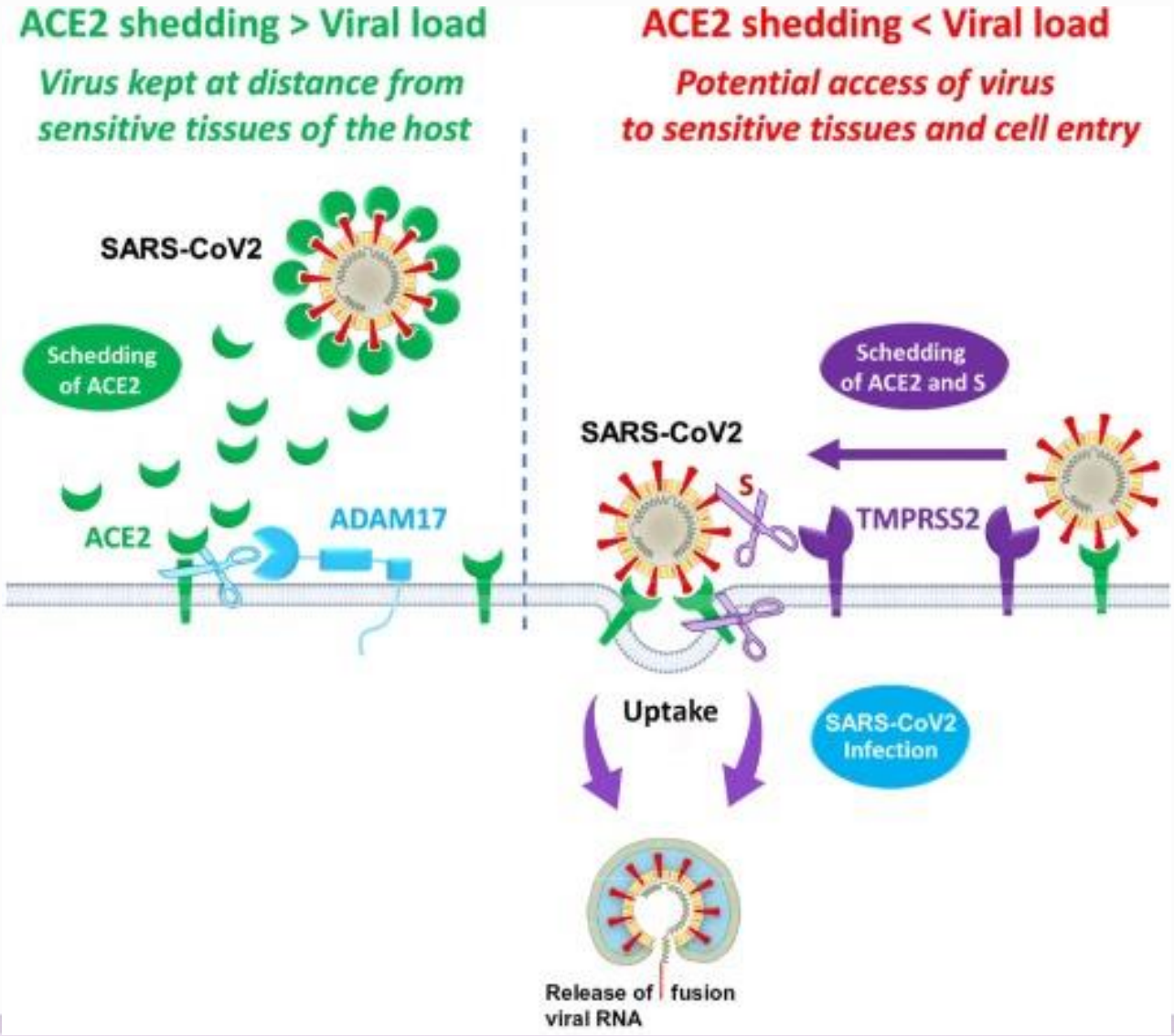
- Genetic variants that affect the expression of one or more genes called Expression quantitative trait loci (eQTL).

- We found that the *ACE2* expression level in 20 tissues can be regulated by 15 unique eQTL variants. They are affected the *ACE2* expression in the nervous tissues, mostly brain, not in the SARS-CoV infection-related main tissues, including lung, kidney, and intestine.

- All of these variants are common (MAF > 0.05) in the Iranian population.

TMPRSS2, a protease with dual functions

We found three missense variants, **Ala650Ser, Arg708Gln**, and Arg708Trp at the ACE2 receptor. They could reduce the affinity of TMPRSS2 for the cleavage of ACE2.



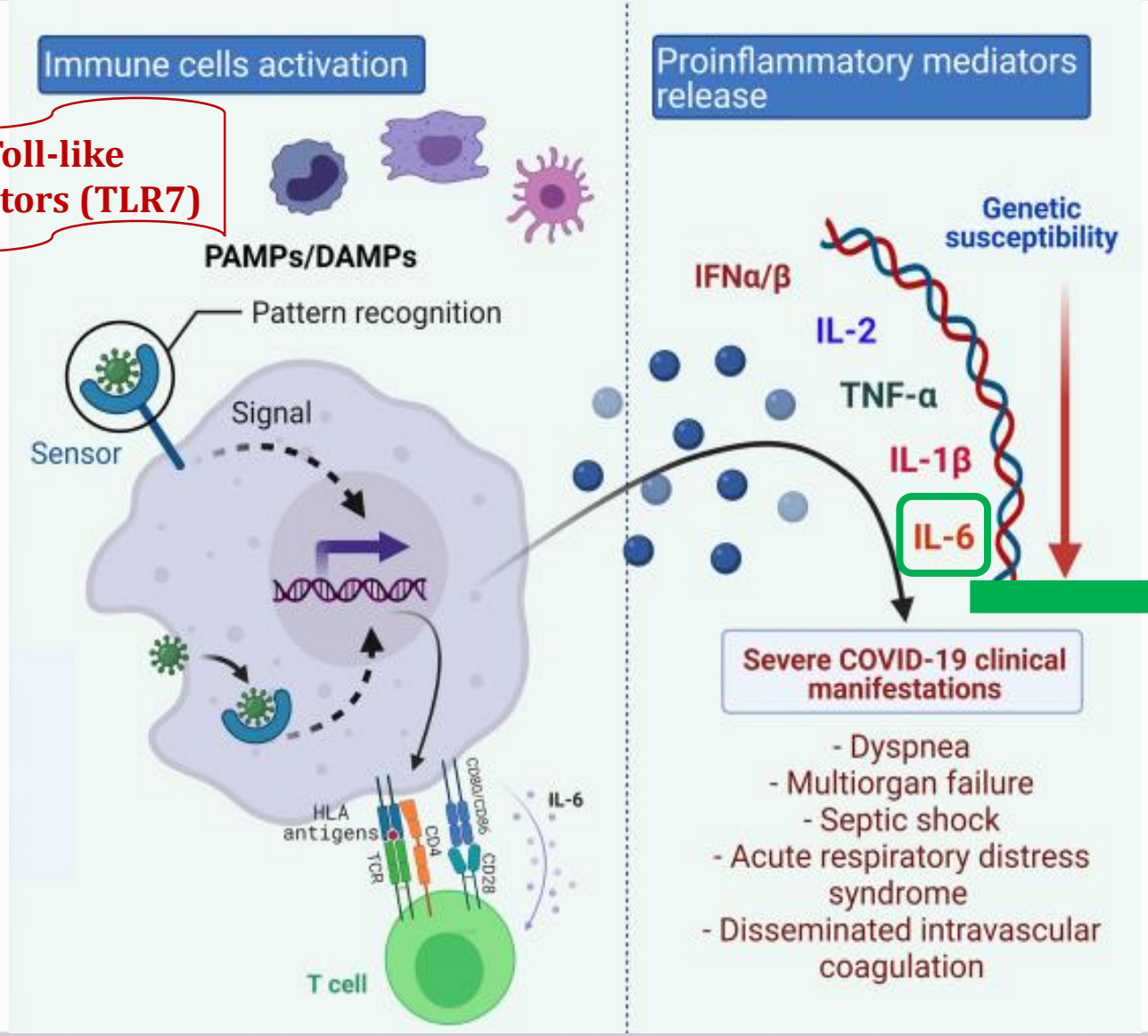
eQTL variants affect the *TMPRSS2* expression level

- ✓ We found 203 eQTL variants influencing the *TMPRSS2* expression in five tissues. The lung, testis, and prostate tissues allocated the highest number of variants, respectively.

- ✓ Almost all variants had the highest allele frequency in Iranian and European populations while the lowest allele frequency variants were recognized in East Asian populations.

- ✓ Homozygous genotype forms of these variants appear to enhance the host susceptibility to SARS-CoV-2 infectivity and pathogenesis via enhancing the *TMPRSS2* expression.

Immunity system-related genes



Appropriate antiviral response

rs1800795

rs1800796

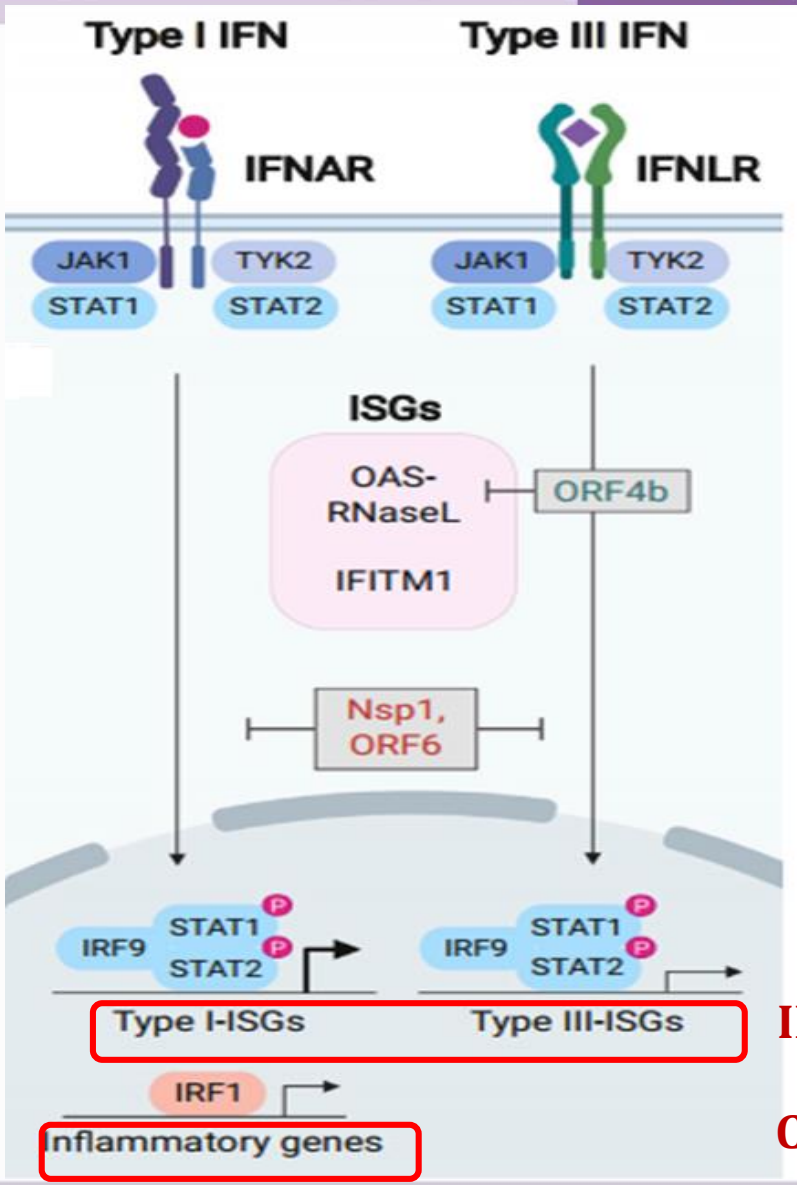
Cytokine storm

Interferon signaling pathway

- Variations of p.Trp73Cys, p.Ser422Arg, p.Pro335del) in IFNAR1 were found in patients hospitalized for life- threatening pneumonia caused by SARS-CoV-2.

- Significant association between critical COVID-19 and intron variant rs2236757 in the *IFNAR2* gene.

- Prescription of interferon beta, ReciGen, highlight the role of interferon in COVID-19 treatment.



IFN-stimulated genes

Cytokines and chemokines

Toll-like receptors variants

- Loss-of-function variants of the **TLR7** (c.2129_2132del; p.Gln710Argfs*18; c.2383G>T; p.Val795Phe) were reported in a case series of four young men from two unrelated families, admitted to the ICU due to critical COVID-19.

- In primary peripheral blood mononuclear cells (PBMC)of the patients, genes coding type I interferon was transcriptionally down-regulated. The levels of IFN-γ, a type II IFN, were also decreased in the patients. So, the TLR7 pathway is an important inducer of type I and II IFN in response to COVID-19.

Our second study

Received: 21 September 2020 | Revised: 13 April 2021 | Accepted: 20 April 2021

DOI: 10.1111/jcmm.16596

SHORT COMMUNICATION

IF:4.5

WILEY

Interplay between SARS-CoV-2 and human long non-coding RNAs

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Abstract

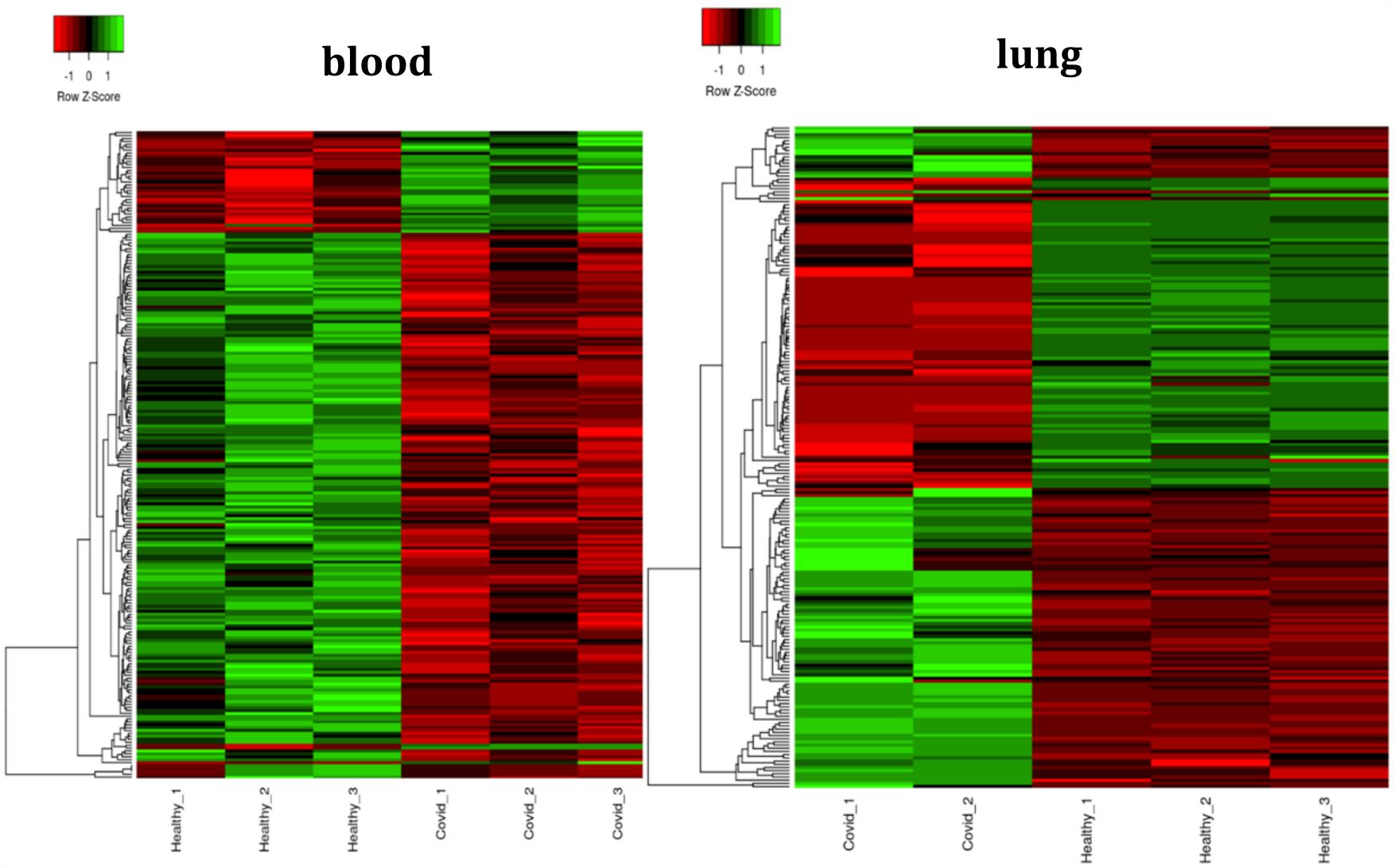
The long non-coding RNAs (lncRNAs) play a critical regulatory role in the host response to the viral infection. However, little is understood about the transcriptome architecture, especially lncRNAs pattern during the SARS-CoV-2 infection. In the present study, using publicly available RNA sequencing data of bronchoalveolar lavage fluid (BALF) and peripheral blood mononuclear cells (PBMC) samples from COVID-19 patients and healthy individuals, three interesting findings highlighted: (a) More than half of the interactions between lncRNAs-PCGs of BALF samples established by three trans-acting lncRNAs (HOTAIRM1, PVT1 and AL392172.1), which also exhibited the high affinity for binding to the SARS-CoV-2 genome, suggesting the major regulatory role of these lncRNAs during the SARS-CoV-2 infection. (b) lncRNAs of MALAT1 and NEAT1 are possibly contributed to the inflammation development in the SARS-CoV-2

Coding and non-coding gene expression profiling in response to COVID-19

Transcriptomic characteristics of bronchoalveolar lavage fluid (BALF) and peripheral blood mononuclear cells (PBMC) in COVID-19 patients, Xiong et al (2020 Mar 31)

- We found that long non-coding RNA (lncRNA) expression were significantly altered in COVID-19 patients compared to healthy individuals in both BALF (lung) and PBMC (blood) samples.

lncRNA expression profiling in response to COVID-19



- lncRNAs of MALAT1 and NEAT1 are possibly contributed to the inflammation development in the SARS-CoV-2 infected cells.

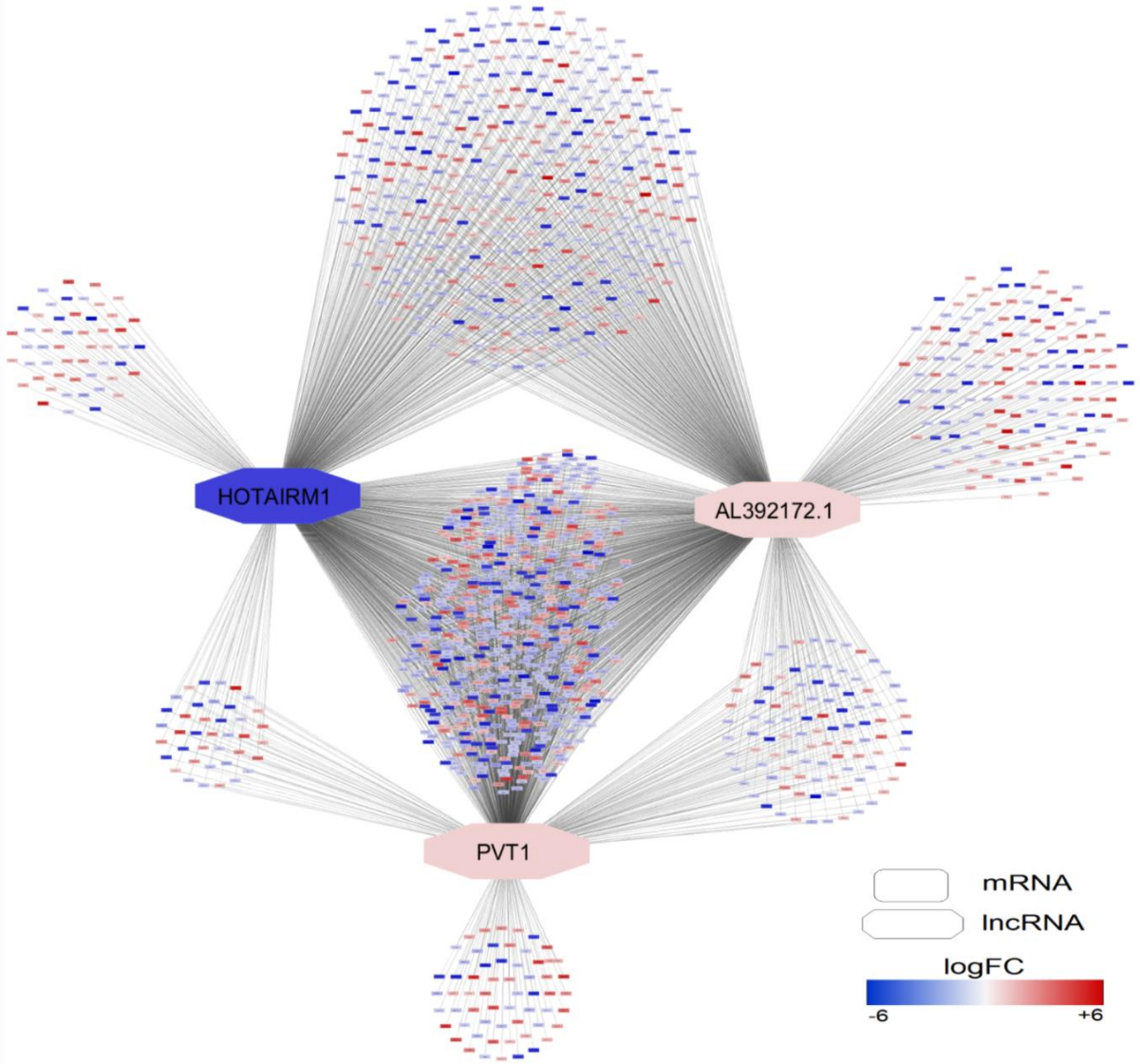
- More than half of the interactions between lncRNAs-PCGs (protein-coding genes) of lung samples established by three trans-acting lncRNAs (HOTAIRM1, PVT1, and AL392172), suggesting the major regulatory role of these lncRNAs during the SARS-CoV-2 infection.

Interaction network between lncRNAs-PCGs (protein-coding genes) of lung samples

HOTAIRM1

PVT1

AL392172



Thank you for your attention!

Any questions?