Bioinformatics analysis reveals genes and pathways shared in COVID-19 disease and comorbidities

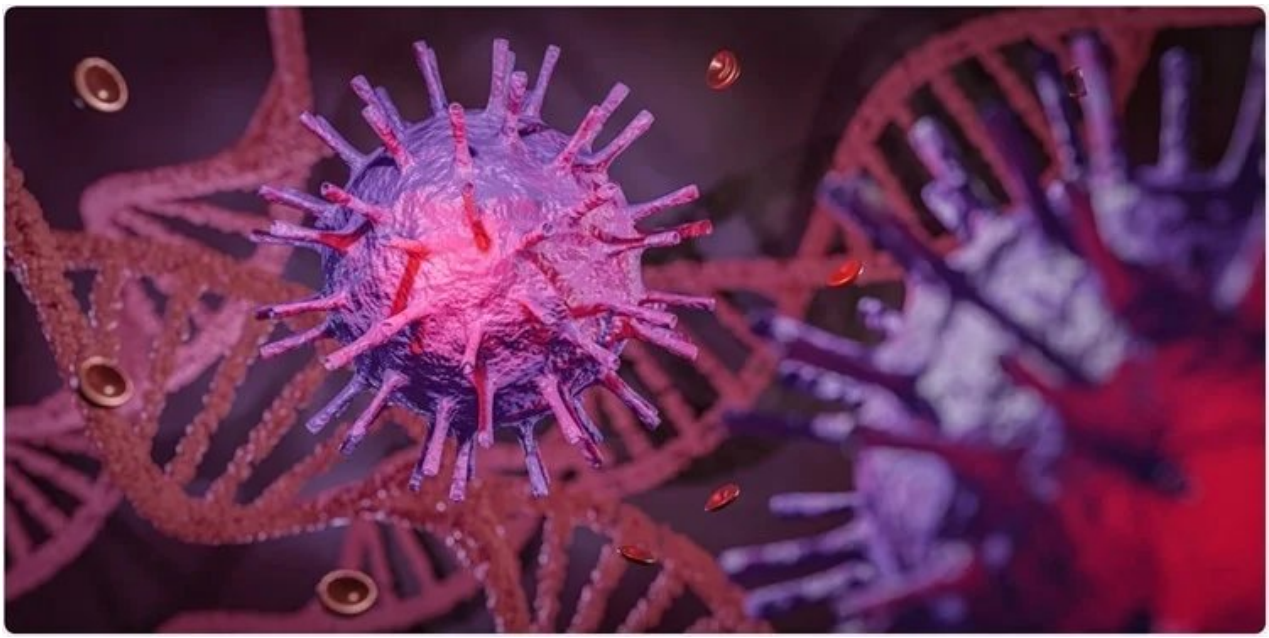
By Lakshmi Supriya, PhD. Sep 23 2020

Using bioinformatics approaches, researchers have identified genes and pathways shared among patients with comorbidities and having severe COVID-19. The research is published on the preprint server *bioRxiv** in September 2020.

Since the beginning of the COVID-19 pandemic, many types of severe responses to the infection have been reported. These include acute respiratory distress syndrome, cytokine release syndrome, and abnormal inflammatory responses.

Several reports have also indicated that in patients with other underlying medical conditions, the severity of the disease is greater. Persons with cardiovascular diseases, diabetes, hepatitis, and diseases of the lungs and kidneys are reported to have a higher COVID-19 disease severity.

There have been efforts to understand the reasons for this greater disease severity from the perspective of the virus as well as the host.



Study: Investigation of COVID-19 comorbidities reveals genes and pathways

coincident with the SARS-CoV-2 viral disease. Image Credit: Studio.c / Shutterstock

Genetics and severity of COVID-19

A team of researchers from The Jackson Laboratory in Maine, USA, hypothesized that investigating the genetics may help understand why COVID-19 is severe in persons with other diseases.

So, the team used genes associated with cardiovascular disease, diabetes, hepatitis, and lung disease obtained from the GeneWeaver Data repository using medical subject headings (MeSH). The genes associated with kidney diseases were derived using the Human Phenotype Ontology (HPO).

They obtained the genes related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from various published reports. All the gene sets were entered into GeneWeaver, a software tool for analysis of genomics data, where the researchers analyzed the gene data.

They first identified the genes shared by the comorbidities. Then, they analyzed the phenotypes associated with the shared genes using mammalian phenotype data from the Mouse Genome Informatics site. They identified the mouse orthologs for the shared human genes using data from the Alliance of Genome Resources.

Next, they performed a pathway enrichment analysis, which is used to analyze biological pathways that are enriched in genes and provides an understanding of the various mechanisms that control the pathways.

Shared genes among common comorbidities

The researchers found eight genes were common to all the five diseases, with 123 genes common to at least four, using the VisuaL Annotation Display tool. Using mouse orthologs for the eight common genes, the team found 762 phenotypes were significantly enriched. These phenotypes were related to T-cells, inflammation or infection, and cardiovascular functions, including abnormal blood clotting.

When they performed the enrichment analysis using the 123 common genes,

they found more than 3,000 phenotypes.

For analyzing enrichment in biological pathways, the team used the Reactome Knowledgebase, which contains information about reactions, their relationships, and the chemicals and genes in those reactions.

For the eight genes common to all the five diseases, they found 103 pathways that were enriched. Some of these pathways include plasma lipoprotein assembly, remodeling, and clearance; platelet activation; and blood clotting. Performing the analysis using the 123 genes common to four of the five diseases also gave a similar result.

All the five diseases shared common physiological characteristics, including blood clotting, cytokine signaling, and plasma lipoprotein biochemistry.

Genes shared with COVID-19

Next, the team analyzed whether any pathways common to the comorbidities were also common with COVID-19. Using genes for COVID-19 from published literature, the authors found that pathways for immune response, angiogenesis, platelet biology, and for signaling mediated by interleukin-4, -10, and -13 were common. These physiological areas are associated with the severity of COVID-19.

The gene STAT3 was highly conserved in nine of the 11 interleukin signaling pathways, and positively regulates transcription of interleukin-6, which controls inflammation. Interleukin-12 is produced in response to infection, via the JAK-STAT pathway, also governed by STAT3, and leads to the production of cells that signal cytokine signaling.

Such a pathway has been proposed before as a reason for the severity of COVID-19, leading to acute respiratory distress. The authors suggest targeting the JAK-STAT pathway may be a promising treatment strategy.

Another common pathway of COVID-19 with the comorbidities relates to platelet biology and blood clotting. Abnormal blood clotting has been observed in patients with severe COVID-19.

The genes HMOX1, APOA1, APOE were common among the five comorbidities.

Levels of APOA1 protein, made by the APOA1 gene, are found to be low in patients with severe COVID-19. APOE gene is involved in lipid binding and cholesterol metabolism. This suggests there could be a genetic factor related to the hemostatic pathway leading to severe disease in patients with any of the five comorbidities.

"Our results show that genes that are shared among five comorbidities associated with severe COVID-19 identify pathways that are consistent with the pathologies associated with the disease," write the authors.

Using mouse orthologs of the shared genes also identified phenotypes linked to severe disease. Thus, experimentally studying mouse models with mutations in these genes and carrying the human SARS-CoV-2 ACE2 receptor could be a path for understanding the genetics causing the severity of the disease.

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Journal reference:

- Dolan, M. E. *et al.* (2020) Investigation of COVID-19 comorbidities reveals genes and pathways coincident with the SARS-CoV-2 viral disease. *bioRvix*. https://doi.org/10.1101/2020.09.21.306720

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