National Jewish Health
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Allergic Inflammation and Viral Infection Change Expression Levels of Genes Crucial to SARS-CoV-2 Infection

Variation in ACE2 and TMPRSS2 Expression Could Influence Severity of COVID-19

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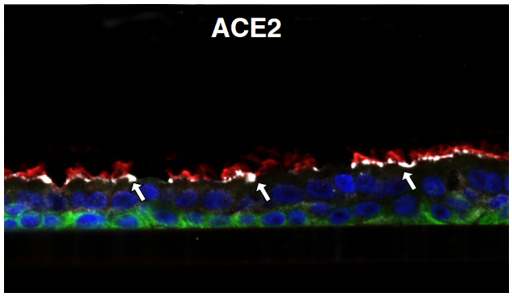
DENVER — One of the most baffling features of COVID-19 is its tremendous variability – from no symptoms to severe illness and death. Researchers at National Jewish Health sought clues to COVID-19 variability by looking at the expression of genes encoding proteins that SARS-CoV-2 uses to enter and infect cells. The researchers report in the journal *Nature Communications* that both allergic inflammation and an immune response to viral infection significantly alter the expression level of those genes, ACE2 and TMPRSS2, in the nasal epithelium where infection first occurs.



SARS-CoV-2 enters and infects epithelial cells when its spike protein binds to the ACE2 receptor on epithelial cells' surface. TMPRSS2 facilitates this process with interactions that make it easier for the spike protein to bind ACE2. Since ACE2 and TMPRSS2 play vital roles in SARS-CoV-2 infection, the amount of mRNA and thus protein, produced in airway cells could affect how much virus enters and infects cells. That, in turn, could influence susceptibility to infection and severity of COVID-19.

"We found that allergic inflammation, driven by the cytokine IL-13, highly upregulates expression of TMPRSS2, but lowers levels of ACE2," said Max A. Seibold, PhD, senior author and associate professor of Pediatrics and the Center for Genes, Environment and Health at National Jewish Health. "The interferon response to viral infection, however, upregulates ACE2 expression with no significant effect on TMPRSS2."

"Allergic inflammation and the inflammatory response to viral infection clearly drive significant changes in the expression of genes crucial for SARS-CoV-2 infection," said biostatistician Satria Sajuthi, PHD, first author on the study. "Whether these factors drive better or worse clinical outcomes remains to be determined. It would be prudent, however, to closely watch individuals with varying levels of IL-13 and interferon for important information on patients' prognosis and course of disease."

The researchers obtained nasal brushings from 695 healthy and asthmatic children previously enrolled in Genes-Environment & Admixture in Latino Americans study (GALA II), an ongoing study of asthma in Latino children and adolescents. They conducted whole transcriptome sequencing on RNA from airway cells obtained from these brushings. They also performed single cell RNA-sequencing and protein measurements using primary culture models of the airway epithelium to determine the precise epithelial cell types expressing these genes and confirm the effects on ACE2 expression also occurred at the protein level.

The children did not have COVID-19, so the researchers could not correlate the protein and RNA levels with severity of disease.

"This research demonstrates how genetic variants in Latino children could lead to a better understanding of respiratory risk factors underlying COVID-19," said James Kiley, Ph.D., director of the Division of Lung Diseases at the

National Heart, Lung, and Blood Institute, part of the National Institutes of Health and one of the study's funders. "But more research is needed to understand how the virus infects cells in the airway and leads to disease, particularly in children."

National Jewish Health is the leading respiratory hospital in the nation. Founded 121 years ago as a nonprofit hospital, National Jewish Health today is the only facility in the world dedicated exclusively to groundbreaking medical research and treatment of patients with respiratory, cardiac, immune and related disorders. Patients and families come to National Jewish Health from around the world to receive cutting-edge, comprehensive, coordinated care. To learn more, visit the media resources page.

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