Study finds genetic clues to pneumonia risk and COVID-19 disparities

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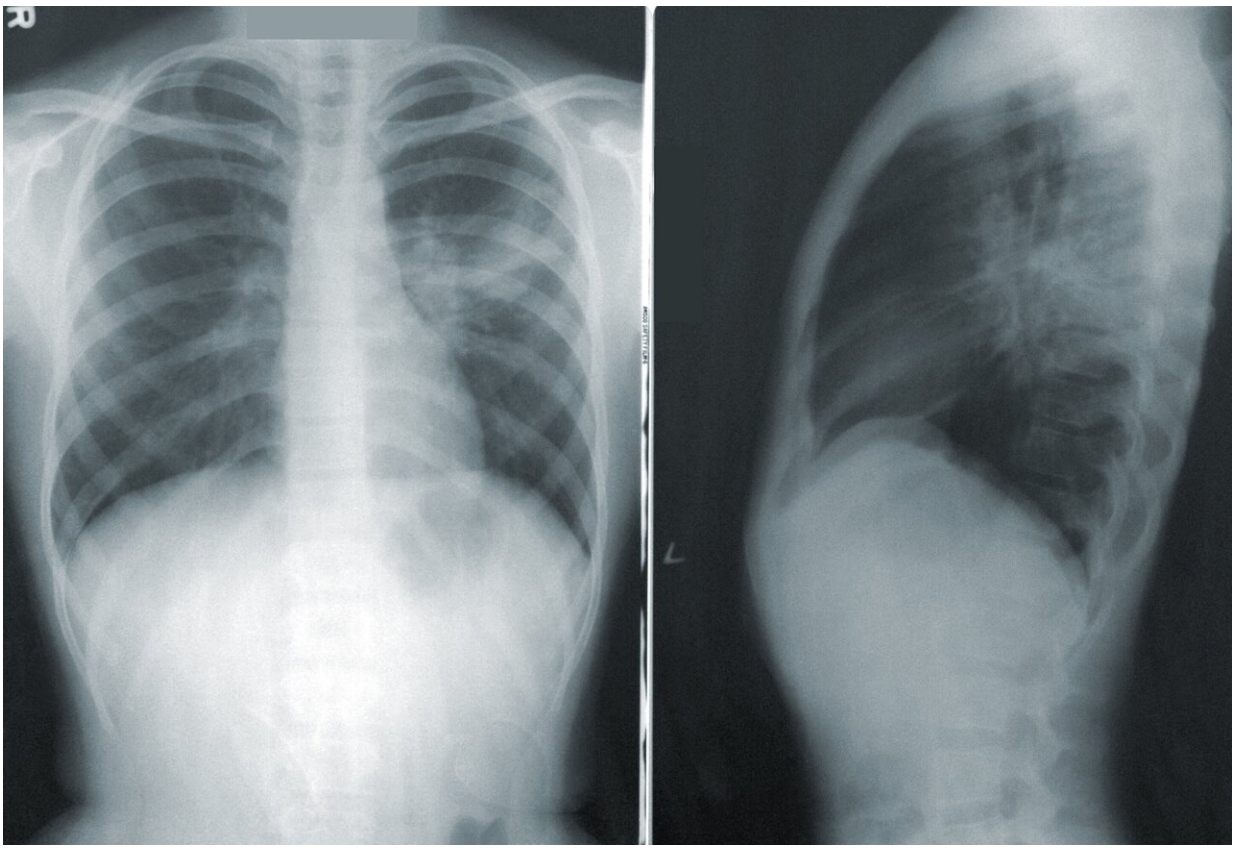

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Researchers at Vanderbilt University Medical Center and colleagues have identified genetic factors that increase the risk for developing pneumonia and its severe, life-threatening consequences.

Their findings, published recently in the *American Journal of Human Genetics*, may aid efforts to identify patients with COVID-19 at greatest risk for pneumonia, and enable earlier interventions to prevent severe illness and death.

Despite the increasing availability of COVID-19 vaccines, it will take months to inoculate enough people to bring the pandemic under control, experts predict. In the meantime, thousands of Americans are hospitalized and die from COVID-19 each day.

"This study is so important because we performed analyses separately in participants of Caucasian ancestry as well as African ancestry to identify genetic risk factors contributing to pneumonia susceptibility and severity," said Jennifer "Piper" Below, Ph.D., associate professor of Medicine and the paper's corresponding author.

"Combined with systemic racism and socioeconomic factors that have been reported by others, these genetic risk differences may contribute to some of the disparities we observe in COVID-19 outcomes," Below said.

The researchers conducted genome-wide association studies (GWAS) of more than 85,000 patients whose genetic information is stored in VUMC's BioVU biobank and which has been linked to "de-identified" electronic health records stripped of personal identifying information. GWAS can identify associations between genetic variations and disease.

With colleagues from the University of North Carolina at Chapel Hill, the University of Texas MD Anderson Cancer Center in Houston, and the Icahn School of Medicine at Mount Sinai in New York, the VUMC researchers identified nearly 9,000 cases of pneumonia in patients of European ancestry, and 1,710 cases in patients of African ancestry.

The strongest pneumonia association in patients of European ancestry

was the gene that causes cystic fibrosis (CF). This disease produces abnormally thick mucus leading to chronic infections and progressive respiratory failure.

In patients of African ancestry, the strongest pneumonia association was the mutation that causes sickle cell disease (SCD), a red blood cell disorder that increases the risk for pneumonia, influenza and acute respiratory infections.

Children with CF and SCD are at particular risk for severe disease if they contract COVID-19.

The researchers found that "carriers" who are unaffected by CF yet carry a copy of the CF gene had a heightened susceptibility to pneumonia, and those who are unaffected by SCD yet carry a copy of the SCD mutation were at increased risk for severe pneumonia.

Further studies will be needed to determine whether these carriers also bear "a silent, heightened risk for poor outcomes from COVID-19," the researchers said.

To identify other genetic variations that increase pneumonia risk, they removed patients with CF and SCD from their analysis, repeated the GWAS, and used another technique called PrediXcan, which correlates gene expression data with traits and diseases in the electronic health record.

This time they found a pneumonia-associated variation in a gene called R3HCC1L in patients of European ancestry, and one near a gene called UQCRFS1 in patients of African ancestry. The molecular function of R3HCC1L is unclear, but deletion of the UQCRFS1 in mice disrupts part of their infection-fighting immune response.

"Although our understanding about the genetic mechanism of pneumonia is still limited, this study identified the novel candidate genes, R3HCC1L and UQCRFS1, and offered an insight for further host genetic studies of COVID-19," said the paper's first author, Hung-Hsin Chen, Ph.D., MS, a postdoctoral fellow in Below's lab.

"Our findings may be applied to identify the individuals with high risk of severe pneumonia and develop a precise treatment for them," Chen said.

More information: Hung-Hsin Chen et al, Host genetic effects in pneumonia, *The American Journal of Human Genetics* (2020). DOI: 10.1016/j.ajhg.2020.12.010

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