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Alternative splicing in lung influences COVID-19 severity and respiratory diseases

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Despite current vaccines and therapeutic options, hospitalization for COVID-19 remains high in many countries. COVID-19 is now a leading cause of death, accounting for more than 6 million deaths worldwide. Thus, there is an ongoing need to identify mechanistic targets for therapeutic development to reduce the risk of severe COVID-19.

Alternative splicing generates functional diversity in isoforms, impacting immune response to infection. In this study, we evaluate the causal role of alternative splicing in COVID-19 severity and susceptibility by applying two-sample Mendelian randomization to *cis*-splicing quantitative trait loci and the results from COVID-19 Host Genetics Initiative.

We identify that alternative splicing in lung, rather than total expression of *OAS1, ATP11A, DPP9* and *NPNT*, is associated with COVID-19 severity. *MUC1* and *PMF1* splicing is associated with COVID-19 susceptibility. Colocalization analyses support a shared genetic mechanism between COVID-19 severity with idiopathic pulmonary fibrosis at the *ATP11A* and *DPP9* loci, and with chronic obstructive lung diseases at the *NPNT* locus.

Finally, we show that *ATP11A, DPP9, NPNT*, and *MUC1* are highly expressed in lung alveolar epithelial cells, both in COVID-19 uninfected and infected samples.

Taken together, our study highlights the importance of alternative splicing in lung for COVID-19 and respiratory diseases, providing isoform-based targets for drug discovery.

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