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


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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