Reply to: Sookaromdee and Wiwanitkit

From the Authors:

On behalf of our coauthors, we thank Drs. Sookaromdee and Wiwanitkit for their interest in our manuscript, "A *MUC5B* gene polymorphism, rs3570590-T, confers protective effects against COVID-19 hospitalizations but not severe disease or mortality" (1). We agree that multiple genetic variants likely contribute to coronavirus disease (COVID-19) susceptibility and severity and wish to highlight the context of our work, which was performed as part of the MVP (Million Veteran Program) COVID-19 Science Initiative and includes participation in the COVID-19 HGI (Host Genetics Initiative), a large-scale, international collaboration to facilitate the rapid identification and dissemination of knowledge on the genetic determinants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease.

The body of work arising from the MVP COVID-19 Science Initiative has included both agnostic (e.g., "hypothesis-free") and targeted approaches. Genome-wide association studies conducted within MVP by Peloso and colleagues (2) confirmed associations between multiple genetic variants, including the ABO blood groups, and COVID-19 positivity. Although no associations with COVID-19 severity were significant at a genome-wide degree in the study by Peloso and colleagues (2), a separate analysis by Verma and colleagues (3) examined associations between leading genetic variants associated with COVID-19 hospitalizations and critical illness in the HGI with preexisting complex diseases in the MVP population through phenome-wide association studies. Complex diseases associated with genetic variants implicated in hospitalization or critical illness included venous thromboembolic diseases, autoimmune conditions, and idiopathic fibrosing alveolitis, an alternative term for idiopathic pulmonary fibrosis (3).

Given this, the intention of the current work (1) was to more deeply characterize the impact of rs35705950-T, a functional variant and established risk factor for idiopathic pulmonary fibrosis, on COVID-19 outcomes within the MVP population. Insights gained beyond the main finding of reduced hospitalizations included a potentially protective effect of rs35705950-T against pneumonia events after COVID-19, an effect specific to COVID-19–positive individuals. Analogous in-depth studies examining genetic variants involved in hematological (4), renal (5), and immune response (6) processes have also yielded novel insights into potential mechanisms which contribute to COVID-19–related outcomes in the MVP cohort. Thus, although we acknowledge that the impact of individual genetic variants should not be considered in isolation, information gained from targeted interrogations can inform hypotheses and complement genome-wide approaches in expanding our collective knowledge on the spectrum of COVID-19 disease. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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