

Association of rare predicted loss-of-function variants of influenza-related type I IFN genes with critical COVID-19 pneumonia

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Letter to the Editor

Infectious disease

To the Editor: Povysil et al. report that “rare loss-of-function variants in type I IFN immunity genes are not associated with severe COVID-19” (1). We disagree with the authors’ interpretation of our data (2) and their own for 6 reasons: (i) Only predicted loss-of-function LOF (pLOF) variants are relevant for comparison between the 2 studies, because, unlike our group, Povysil et al. did not test variants experimentally. The relevant proportion in our data is therefore not 23/659, or 3.5%, but 9/659, or 1.36%; whereas theirs is 1/713, or 0.14%. (ii) Our definitions of “severe/critical” disease are different: we defined critical disease as having severity grades 6–10 according to the WHO scale (3), whereas Povysil et al. restricted their recruitment to grades 7–10 (i.e., excluding patients on high-flow oxygen, who were considered in our study). Their cohort of “mild” cases may therefore have included severe COVID-19 cases (grade 6), such as perhaps the TLR3 pLOF carrier designated as having mild disease. (iii) The controls in the work by Povysil et al. comprised individuals from the general population, without depletion of COVID-19 genetic risk factors, whereas we included paucisymptomatic and asymptomatic infected subjects (grades 1–3) as controls. Consequently, the power computation shown in their Figure 1 is based on an incorrect hypothesis about the odds ratio, which would be expected to be [...]

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patients with autoantibodies against type I IFN, which account for at least 10% of critical cases; these autoantibodies are much more frequent in patients older than 60 years, particularly men (4).

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