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

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 lower when using general population controls (as they did) than when using paucisymptomatic and asymptomatic infected individuals (as we did). (iv) The ethnic origin of the patients differs between the 2 studies: 58% of our 659 patients (and 8 of our 9 pLOF carriers) were European, versus only 10% of their 713 patients with severe disease (and the pLOF carrier was East Asian). (v) Age is a key factor neglected in their comparison: our sample was much younger (mean age, 51.8 years) than theirs (mean, 65.9 years), and 7 of our 9 pLOF carriers were younger than 60 years. We performed a comparison stratified by age (<60 versus ≥60 years), and no significant difference in pLOF proportion was found between the 2 studies, even ignoring the only patient carrying a pLOF they identified (of unknown age): 7/458 in our sample versus 0/192 in their sample ($P = 0.11$, Fisher's exact test) for patients younger than 60 years, and 2/201 versus 0/521 ($P = 0.07$) for patients at least 60 years old. (vi) Finally, and crucially, the authors did not exclude 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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