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

Gundula Povysil, … , David B. Goldstein, Krzysztof Kiryluk

Letter to the Editor   In-Press Preview   Infectious disease

The authors reply: We appreciate the interest of Dr. Zhang and colleagues in our manuscript. The main difference between our publication and that of Zhang et al. (1), was that we assessed all rare predicted loss-of-function variants (pLOFs) meeting the same criteria in cases and controls, which is a well-established paradigm in the field (2). On the other hand, Zhang et al. included specific variants which were experimentally confirmed only in cases, but not controls, precluding a valid case-control comparison.

We matched patients as closely as possible to the previous study, and the inclusion of more severe cases (WHO grades 7-10) should only strengthen the signal against population controls. The use of population controls is standard in such settings and has minimal impact on power, because only a small proportion of individuals exposed to SARS-Cov-2 develop severe disease (3). Additionally, for the pLOF model we report adequate power even for an odds ratio of 5.5, which is considerably lower than the one reported by Zhang et al. We tested the same dominant model as Zhang et al., even though LOF variants in these genes have only been reported to cause disease under recessive inheritance (4).

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We have serious concerns about confounding by ancestry in the analysis by Zhang et al. in which the pLOF carriers were mostly European, but functionally validated missense variants were found in various nationalities from Asia, Europe, Latin America, and the Middle East. Because the rates of pLOFs vary considerably across populations, adjusting for only 3 principal components of ancestry in rare-variant association tests of multi-ethnic cohorts does not provide adequate control for population structure.

While we noted that age differences may contribute to the discrepancies between the two studies, Zhang et al. do not discuss the role of age in the interpretation of their results stating: "Inborn errors of TLR3- and IRF7-dependent type I IFN immunity at eight loci were found in as many as 23 patients (3.5%) of various ages (17 to 77 years) and ancestries (various nationalities from Asia, Europe, Latin America, and the Middle East) and in patients of both sexes." We also note that the patients with autoantibodies were not excluded from the primary analysis by Zhang et al., but this was done only in the post-hoc analysis.

Most importantly, our negative findings are in full agreement with the recently published independent study of 586,157 individuals, including 20,952 cases of COVID-19 (4,928 hospitalized and 1,304 requiring ventilation or resulting in death) (5). There were no significant associations with any of the 13 candidate genes examined either individually or in aggregate, or when comparisons included all hospitalized cases or only the most severe cases. Indeed, none of the associations displayed even marginal significance. Therefore, consistent with our study, these findings do not support substantial contributions of inborn errors in type I IFN immunity to COVID-19 severity.

These negative results underscore the importance of proper study design, selection of appropriate genetic models, adequate control for genetic ancestry, and adherence to unbiased methods for genetic discovery rather than focusing only on a candidate biological pathway.

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The authors declare that no conflict of interest exists.