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Genomic variation underlies the severity of COVID-19 clinical manifestation

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Motivation and Aim: COVID-19 is characterized by a wide spectrum of clinical phenotypes ranging from complete absence of perceivable symptoms to severe disease manifestations. COVID-19 susceptibility, severity and recovery has demonstrated individual as well as population specific variations. Several studies have attributed this variation to the hosts' genetic make-up. As a follow-up to our previous study [1], here we performed an Exome-Wide Association Study (EWAS) employing a novel and unpublished whole exome data from University of Sienna, Italy.

Methods: The dataset consisted of 2,960 COVID-19 patients of various degrees of disease presentations. We restricted our analysis to 2,692 Europeans present in the dataset by performing principal component analysis with individuals from 1000 genome project. We performed GWAS in two cohorts. In cohort-1, the non-hospitalized patients were employed as controls and all hospitalized patients were employed as cases, and in cohort-2, the non-hospitalized patients and patients who did not require any respiratory support were employed as controls and the rest were employed as cases. We further performed ancestry analysis using ADMIXTURE v1.3.

Results: We identified 1501 and 362 genetic variants that were significantly distinct (Multiple-testing corrected $P<0.001$) between cases and controls in cohort-1 and cohort-2 respectively. Among these variants, 117 were common to both cohorts, which were found to be associated with pathways governing host immunity, such as interferon gamma signaling, toll like receptor cascade, antigen processing, cross presentation of soluble antigens, G-protein coupled receptor pathways (GPR) and COVID-19 comorbidities, such as lipid metabolism. We identified three novel loci in X chromosome, one of which overlaps with our previous study and is associated with extra-cellular matrix organization and is likely linked to the pulmonary fibrosis among severe COVID-19 patients. We further identified novel SNVs in chrX including one at ACE2, the receptor of SARS-CoV-2. Further, hospitalized patients revealed significantly larger Central European ancestry (p-value = 0.03) and highly significantly larger Western European ancestry (p-value = 0.002) compared to their non-hospitalized counterparts.

Conclusion: Overall, our study indicated the likely association between polymorphisms in chrX and the severity of COVID-19 disease presentation and potential crucial role of GPR signaling in severe disease outcomes. Our study further revealed the hospitalized patients have higher Central and Western European ancestry fractions compared to their non-hospitalized counterparts.

References

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