Human Leukocyte Antigen (HLA) Associated COVID-19 Outcomes in the All of Us Dataset

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COVID-19 remains a public health threat, and thus it is important to identify those who are at risk of severe disease. The primary objective of this study is to investigate the relationship between human leukocyte antigen (HLA) alleles to COVID-19 clinical severity, specifically: hospitalization, mortality, pneumonia by COVID-19, Long COVID, and clinical lab values via COVID-19 antibody concentrations.

We conducted a retrospective cohort study utilizing the Controlled Tier dataset to evaluate the microarray genotyping array data and electronic medical records of included participants. This study was approved by the Institutional Review Board at Louisiana State University Health Sciences Center, IRB number 7407. The base population was defined as any patient with a positive SARS-CoV-2 RNA test and global array genomic data. Long COVID definitions were developed by the N3C consortium and refined in house and controlled against ICD-10 code U09.9. A total of 109,552 patients ((1) a positive COVID-19 test (n=20,872), (2) a negative COVID-19 test (n= 88,680), (3) both a positive test and a diagnosis code for Pneumonia due to COVID-19 (J12.81) or lower respiratory infection caused by SARS-CoV-2 (n= 1,079), (4) a negative test and a diagnosis code for Pneumonia due to COVID-19 or lower respiratory infection caused by SARS-CoV-2 (n= 1,564), (5) a positive test and a diagnosis code for Long COVID (U09.9) (n= 509), and (6) a negative test and a diagnosis code for Long COVID (n= 990)) are included in this study. HLA Class I and Class II alleles have been imputed from a global diversity reference panel utilizing the HI-BAG "R" package.

Our study is characterized by several key strengths. We conducted a detailed analysis of the HLA alleles associated with COVID-19 clinical severity in the AllofUs dataset, as well as COVID-19 related survey answers, from 109,552 participants. Compared to Long COVID and COVID-19 Test cohorts, individuals who developed pneumonia or a lower respiratory infection caused by SARS-CoV-2 exhibited higher prevalence of co-morbidities and a higher prevalence of individuals reported to regularly take immunosuppressant medications. In contrast, participants diagnosed with Long COVID were more likely to be women and reported greater adverse reactions to the COVID-19 vaccine, particularly with symptoms of tiredness, swelling, muscle pain, and headaches. Notably, we identified several novel alleles associated with COVID-19 clinical severity while also confirming previously re-ported allelic associations. Finally, we identified 118 HLA allelic frequencies from the National Bone Marrow Donor Program that may be over- or underestimated. The goal of this study we hope to determine the relationship between imputed HLA Class I and Class II alleles and COVID-19 clinical outcomes documented in electronic health records seen within the All of Us dataset. The overall intent is to determine HLA alleles at risk of or protected from severe COVID-19 clinical outcomes, specifically: pneumonia by COVID-19 and Long COVID. We hope this study will accelerate personalized care of COVID-19.