Genetics and the COVID-19 pandemic

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With the COVID-19 pandemic still raging worldwide, members of the American Society of Human Genetics (ASHG) are working to understand how the virus spreads and infects people, why there is so much variability in susceptibility and severity, and where to look for potential therapeutics. Researchers presented the results of several

studies relevant to the current pandemic at the ASHG 2020 Virtual Meeting.

COVID-19 symptoms vary widely, ranging from asymptomatic in some patients to fatal in others. Elucidating the role of human genetic variation could result in a better understanding of susceptibility to infection as well as differences in patient presentation and outcomes.

Three studies addressed human genetics and COVID-19 susceptibility and severity. In the first, Jack Kosmicki, Regeneron Genetics Center, and colleagues presented the results of the largest trans-ancestry exome sequencing study of COVID-19 to date. In a replication of previous findings, the researchers identified the 3p21.31 locus and suggested it contributes to variability in severity. The group failed to replicate an association between COVID-19 and the ABO locus, suggesting that the previous finding may have been a false positive. Beyond previously reported associations, Kosmicki and colleagues also identified three novel loci and three genes associated with COVID-19.

In the second, Andrea Ganna, Institute for Molecular Medicine Finland, and colleagues reported a meta-analysis from the COVID-19 Host Genetics Initiative, a collaborative, international effort to bring together the human genetics community to generate, share, and analyze data related to COVID-19. They identified a genetic variant on chromosome 3 that was strongly associated with disease severity but not susceptibility. Like all of the Initiative's results, these are immediately available on its website without any restriction of use.

The third study, presented by Gita Pathak, Yale University, suggests the involvement of several biological mechanisms in COVID-19 induced hospitalization. In addition to identifying six COVID-19-associated genes in two chromosomic regions, the researchers uncovered associations with laboratory readings—such as LDL cholesterol and

cortisol levels and monocyte count—that are consistent with markers of inflammation. Together, these studies point to exciting areas for future research. For instance, all three groups identified chromosome 3 as a susceptibility locus but further work is needed to work out the mechanism.

In another COVID-19 related study, A. Rouf Banday, National Cancer Institute, National Institutes of Health, reported the discovery of a novel variant of the enzyme ACE2, which the virus SARS-CoV-2 uses to enter target cells. The researchers showed that this variant called dACE2, but not ACE2, is induced by interferons and viral infections, including SARS-CoV-2. The findings are important to consider for future therapeutic strategies and understanding susceptibility and outcomes of COVID-19.

Brendan O'Connell, Oregon Health & Science University, and colleagues demonstrated that rapid sequencing of viral genomes can enable the identification of specific transmission chains within a community by tracing mutations that arise over time. The researchers determined the number of introductions and spread of COVID-19 in Oregon during the first six months of the outbreak. Overall, the data strongly support the major source of new viral introductions in Oregon are from domestic travel.

Finally, Tomiko Oskotsky, University of California San Francisco, discussed the application of a computational drug repositioning pipeline to identify existing drugs that may have novel therapeutic uses in COVID-19. The results thus far are encouraging, with validation experiments showing that nine of the 12 hits tested to date have measurable antiviral activity against SARS-CoV-2.

More information: Olusegun O. Onabajo et al. Interferons and viruses induce a novel truncated ACE2 isoform and not the full-length SARS-

CoV-2 receptor, *Nature Genetics* (2020). DOI: 10.1038/s41588-020-00731-9 , www.nature.com/articles/s41588-020-00731-9

Banday, A.R., et al. (Date). Abstract: The discovery of a novel primate-specific and inducible truncated isoform of ACE2 and its implications for SARS-CoV-2 infection. Presented at the American Society of Human Genetics 2020 Virtual Meeting.

Ganna, A., et al. (Date). Abstract: The COVID-19 host genetics initiative identifies genetic factors associated with COVID-19 susceptibility, severity, and outcomes. Presented at the American Society of Human Genetics 2020 Virtual Meeting.

Kosmicki, J., et al. (Date). Abstract: Trans-ancestry imputation and exome sequencing of 868,021 individuals identifies 4 loci and 3 genes associated with Covid-19 susceptibility and hospitalization. Presented at the American Society of Human Genetics 2020 Virtual Meeting.

O'Connell, B., et al. (Date). Abstract: Genomic surveillance of SARS-CoV-2 in Oregon from February-July 2020 identifies at least 25 independent introductions, transmission dynamics of a healthcare workplace superspreading event, and recurrent deletions removing ORF7a from the viral genome. Presented at the American Society of Human Genetics 2020 Virtual Meeting.

Ostotsky, T., et al. (Date). Abstract: Transcriptomics-based drug repositioning pipeline identifies therapeutic candidates for COVID-19. Presented at the American Society of Human Genetics 2020 Virtual Meeting.

Pathak, G., et al. (Date). Abstract: Integrative analyses with large-scale COVID-19 GWAS identifies susceptibility genes underlying

hospitalized outcomes. Presented at the American Society of Human Genetics 2020 Virtual Meeting.

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