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SPECIAL ARTICLE

The intersection of genetics and COVID-19 in 2021: preview of the 2021 Rodney Howell Symposium

Sonja A. Rasmussen[1] ✉, Noura S. Abul-Husn[2], Jean-Laurent Casanova[3,4,5,6], Mark J. Daly[7,8], Heidi L. Rehm[9,10] and Michael F. Murray[11]

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Coronavirus disease 2019 (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first identified in late 2019 in China, has spread quickly throughout the world, resulting in significant morbidity and mortality. As of 21 January 2021, over 96 million cases and over 2 million deaths have occurred globally, with over 24 million cases and over 400,000 deaths in the United States alone (https://coronavirus.jhu.edu/). In addition to the direct effects of COVID-19 on illnesses and deaths, interventions to decrease transmission of SARS-CoV-2 have had devastating effects on preventive health services, education of children, economies of many countries, and biomedical research outside of COVID-19, among others. The recent availability of safe and effective COVID-19 vaccines is encouraging; however, it is expected that herd immunity and a return to normal life are several months away.

Genetics in Medicine has organized the Rodney Howell Symposium for the upcoming 2021 American College of Medical Genetics and Genomics Meeting (April 2021), co-chaired by Drs. Robert Steiner and Michael Murray, to highlight some areas where the COVID-19 pandemic and the human genetics community have intersected. The pandemic year of 2020 has left a pervasive mark on all human communities, and the human genetics and genomics community is no different; this is made apparent by the breadth of topics covered by this expert group. The following are brief summaries of five presentations to be discussed at the Symposium on 16 April entitled "2021 COVID-19 State of the Science."

A GLOBAL EFFORT TO DEFINE THE HUMAN GENETICS OF PROTECTIVE IMMUNITY TO SARS-COV-2: JEAN-LAURENT CASANOVA

Interindividual clinical variability is the rule in the course of any human infection, and SARS-CoV-2 infection is no exception. Immense interindividual clinical variability in the course of SARS-CoV-2 infection has been observed, ranging from silent or benign infection in >95% of individuals to life-threatening pneumonia requiring intensive care in less than 0.5% of infected subjects. Other severe clinical manifestations are rarer and include COVID-19-related Kawasaki disease. Epidemiologists rapidly identified age as a major risk factor for critical pneumonia, with a risk of life-threatening disease sharply increasing from the age of 65 years onward, whereas, conversely, Kawasaki disease was observed almost exclusively in patients under the age of 20 years. The other risk factors identified to date, such as sex and comorbidities, play a much more modest role, with odds ratios typically less than 2.[1] The COVID Human Genetic Effort (www.covidhge.com) was launched in March 2020 to test the hypothesis that some patients may suffer from life-threatening pneumonia or Kawasaki disease because of single-gene inborn errors of immunity.[2] The aim of this consortium has remained the discovery of monogenic causes of life-threatening forms of COVID-19, with the hope that these discoveries, even in rare patients, might pinpoint disease mechanisms that might also operate and could be targeted by other means in patients without monogenic lesions.

The first specific hypothesis tested was that critical COVID-19-associated pneumonia and critical influenza-associated pneumonia are allelic conditions. Previous studies had shown that inborn errors of Toll-like receptor 3 (*TLR3*), interferon regulatory factor 7 (*IRF7*), and interferon regulatory factor 9 (*IRF9*) underlie critical influenza-associated pneumonia in previously healthy patients. Biochemically and immunologically related inborn errors had been shown to underlie other viral illnesses. Known autosomal dominant and autosomal recessive inborn errors of TLR3- and IRF7-dependent type I interferon (IFN) immunity were identified in 15 patients with critical COVID-19 pneumonia, including two unrelated patients with autosomal recessive IRF7 deficiency and two unrelated patients with autosomal recessive IFN-α/β receptor 1 (*IFNAR1*) deficiency.[3] Eight other patients were heterozygous for deleterious variants of genes for which biallelic pathogenic variants are known to underlie severe influenza and/or other viral illnesses. Inborn errors of TLR3- and IRF7-dependent type I IFN immunity impair innate and intrinsic immunity to SARS-CoV-2 ex vivo and in vitro, respectively. Cells from patients with autosomal recessive IRF7 deficiency produce only minimal amounts of type I IFNs, whereas those from patients with autosomal recessive IFNAR1 deficiency do not respond to type I IFNs. Surprisingly, these four patients were adults aged 28 to 50 years who had never been hospitalized for severe viral illnesses before COVID-19. These findings suggest that type I IFNs are essential for protective immunity against SARS-CoV-2 but are redundant, at least in some individuals, for host defense against many other viruses including influenza virus.

These findings led to another hypothesis: that critical COVID-19-associated pneumonia may occur in some patients due to the presence of pre-existing autoantibodies against type I IFNs. These autoantibodies were first described in the early 1980s in patients

[1]Departments of Pediatrics, Obstetrics and Gynecology, and Epidemiology, University of Florida College of Medicine and College of Public Health and Health Professions, Gainesville, FL, USA. [2]Institute for Genomic Health, Department of Medicine, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [3]St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA. [4]Howard Hughes Medical Institute, New York, NY, USA. [5]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM, Necker Hospital for Sick Children, Paris, France. [6]Imagine Institute, University of Paris, Paris, France. [7]Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland. [8]Broad Institute of MIT and Harvard, Cambridge, MA, USA. [9]Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. [10]Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA. [11]Department of Genetics, Yale School of Medicine, New Haven, CT, USA. Special Article *Genetics in Medicine* Presents: Spring 2021 COVID-19 State of the Science 2021 ACMG Annual Clinical Genetics Meeting [April 13–16, 2021]. ✉email: Sonja.Rasmussen@peds.ufl.edu

treated with type I IFN, and in patients with systemic lupus erythematosus, thymoma, or autoimmune polyendocrinopathy type I (APS-I). However, they have never before been associated with viral illnesses. At least 10% of patients with critical COVID-19-associated pneumonia carried high titers of neutralizing autoantibodies against type I IFNs, whereas these antibodies were absent from infected patients who were asymptomatic.[4] The global prevalence of these autoantibodies in the general population is very low (<0.3%). These autoantibodies were neutralizing at high dilutions, abolishing the protective effect of even high concentrations of type I IFN against SARS-CoV-2 in vitro. Remarkably, these autoantibodies were found preferentially in men (95%) and in the elderly (half the patients with autoantibodies against type I IFN were older than 65 years of age). Collectively, these two studies showed that the disruption of type I IFN immunity by single-gene inborn errors or by neutralizing autoantibodies can underlie life-threatening COVID-19 pneumonia. They further suggest a two-step model of pathogenesis, with defects of type I IFN immunity in the first few days of infection with SARS-CoV-2, in these and perhaps other patients, leading to the excessive inflammation characteristic of severe COVID-19.[1]

THE COVID-19 HOST GENETICS INITIATIVE: A WORLDWIDE PANDEMIC RESEARCH COLLABORATION: MARK DALY

The COVID-19 Host Genetics Initiative (www.covid19hg.org) was launched in spring 2020 to bring together the international human genetics community to learn about the genetic determinants of COVID-19 susceptibility, severity, and outcomes.[5] The basis of this worldwide collaborative was to ultimately inform the classification of individuals at unusually high or low risk, to generate hypotheses for drug repurposing, and to contribute to global knowledge of the biology of SARS-CoV-2 infection and disease. This has been achieved by providing an environment for sharing of resources to facilitate COVID-19 host genetics research, organizing analytical activities across studies to identify genetic determinants of COVID-19 susceptibility and severity, and providing a platform to share the results from such activities with the broader scientific community.

This initiative has specifically contributed to several published genome-wide association studies by releasing global meta-analyses immediately and publicly for all to use, including an early study of more than 1,600 cases of severe COVID-19 with respiratory failure from Italy and Spain,[6] which provided the first evidence of a 3p21.31 gene cluster and the ABO locus in patients with COVID-19 with respiratory failure, and a larger study from the United Kingdom of 2,200 patients admitted to the intensive care unit,[7] which implicated several new genes including *TYK2*, *DPP9*, and the *OAS1/2/3* gene cluster. By the end of 2020, 48 groups around the world had contributed genetic association results to the COVID-19 Host Genetics Initiative and results publicly released in January 2021 provide the largest view of both severity and susceptibility, with more than 14,000 hospitalized cases and nearly 50,000 polymerase chain reaction (PCR)-positive cases overall included. The global diversity of participation in this effort has already yielded additional insights; for example, variation affecting the expression of FOXP4 and severe COVID-19 outcomes is far more common in East and South Asian and Hispanic/Latino populations than in Europe.

GENOMICS, DIVERSE POPULATIONS, AND HEALTH DISPARITIES IN THE TIME OF COVID-19: NOURA ABUL-HUSN

The disproportionate burden of COVID-19 incidence and severity among racial/ethnic minority populations in the United States has been observed since early stages of the pandemic (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/racial-ethnic-minorities.html). Recognizing and addressing the roots of COVID-19 health disparities are imperative to enacting equitable health care across populations. Population-level disparities in COVID-19 are partly explained by differential disease incidence, prevalence of pre-existing comorbidities, social determinants, and other identified risk factors.[8] For the most part, COVID-19 population disparities have little to do with host genomic factors. However, failure to engage ancestrally diverse populations in COVID-19 genomic research could perpetuate existing health disparities. Efforts to include diverse participants in large-scale genomic studies of COVID-19 susceptibility and severity are needed to discover new gene–disease associations and generate knowledge that benefits all populations and have widespread applicability.[9,10] Host genomic factors having different allele frequencies in human populations as a result of their ancestral geographic origins may be uncovered. Recognizing that structural racism contributes to COVID-19 health disparities, the genetics community needs to contextualize and accurately communicate links identified between host genomic factors, genetic ancestry, and COVID-19 outcomes, particularly in underserved and underrepresented populations.

SCALING SARS-COV-2 TESTING TO SERVE THE NATION: HEIDI REHM

A critical aspect of managing the global COVID pandemic has been the use of testing to detect the SARS-CoV-2 virus. The main types of testing include nucleic acid testing or antigen testing to detect live virus as well as antibody testing to detect the body's immune response to the virus. Although multiple nucleic acid testing approaches are available,[11] reverse transcription PCR (RT-PCR) testing is the most commonly used with both commercial kit-based platforms and laboratory developed tests (tests designed, manufactured, and used in a single laboratory) available (www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covidinvitrodev). Antigen testing is becoming more widely available and has the advantage of rapid turnaround time and can be used at the point of care, although disadvantages include reduced sensitivity for individuals with low levels of virus making it more appropriate for surveillance than diagnosis.[12] Antibody testing is also available, although it is less useful for diagnosis and surveillance given the delay in seroconversion in an individual who is infected. It is most widely used to assess population-level rates of infection.

Many studies have been published to assess the analytical sensitivity and specificity of testing and have found RT-PCR-based methods to have very high specificity and reasonable sensitivity with sensitivity varying based on the quality of specimen sampling and most importantly, the time-point of the stage of infection.[13] A key challenge for testing has been the wide range in viral load, which can span many orders of magnitude from 100 copies per milliliter to 10 billion copies per milliliter, with extremely high titers. Furthermore, the range of viral load has been found to be the same across both symptomatic and asymptomatic individuals,[14] underscoring the critical need for surveillance testing and contact tracing to control spread, given the inability to rely on symptom-based screening.

THE SCIENCE BEHIND COVID-19 EFFECTS IN PREGNANT PERSONS AND CHILDREN: SONJA RASMUSSEN

Pregnant persons and children have been at increased risk for serious complications during previous outbreaks, including 2009 H1N1 influenza pandemic,[15] requiring a special focus on these populations as part of the public health response. Data continue to emerge about the effects of SARS-CoV-2 infection on pregnant persons and children. Based on a recent large study, pregnant persons were more likely to be admitted to an intensive care unit, to require invasive ventilation, to receive extracorporeal membrane oxygenation, and to die than nonpregnant women of

reproductive age.[16] The reasons behind these increased risks is unknown, although changes in a pregnant woman's immune system that allow her to tolerate a fetus with foreign paternal antigens could be partially responsible. Change in lungs and heart that occur during pregnancy could also increase the risk of severe COVID-19 disease among pregnant persons. Whether infants born to women infected with SARS-CoV-2 during pregnancy are at increased risk of adverse outcomes is still under investigation.[17] Intrauterine transmission of SARS-CoV-2 can occur, but appears to be rare. This could be related to minimal expression by the placenta of the angiotensin converting enzyme 2 (ACE2) receptor and the transmembrane serine protease 2 (TMPRSS2), both necessary for entry of SARS-CoV-2 into cells.[18]

Most SARS-CoV-2 infections in children are mild or asymptomatic; however, some children, often those with underlying conditions including some with genetic conditions,[19] have become severely ill, requiring admission to an intensive care unit, and a few children have died.[20,21] Why most children are less severely affected is unknown, although hypotheses to explain the findings include difference in innate and adaptive immunity, pre-existing immunity to other coronaviruses, differing density or distribution of ACE2 receptors and TMPRSS2, protective off-target effects of live vaccines, lower levels of inflammatory cytokines, and lower levels of exposure to SARS-CoV-2.[22,23] A few children develop a severe illness similar to Kawasaki disease (also called multisystem inflammatory syndrome in children [MIS-C]) 2–4 weeks following infection with SARS-CoV-2. Children who are black or Hispanic appear to be at increased risk for development of this illness; whether this is due to the increased frequency of SARS-CoV-2 infections in the black and Hispanic communities or other reasons is unknown.[24] Additional studies on the effects of COVID-19 on pregnant persons and children and how to mitigate those effects are needed.

Some of the early projections for what to expect in the "genomic era"[25] have been reinforced during the COVID-19 pandemic. In this pandemic year, genomic information and sequencing technologies have been used to diagnose individuals with SARS-CoV-2, define features of viral transmission and epidemiology, and understand disease pathology. The contributions from members of the human genomics community have been diverse in nature and international in scale. As the pandemic comes under better control in the months ahead the contributions and lessons learned are expected to be enduring in nature.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to S.A.R.

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