Written abstracts (300 words or less) along with a description (150 words or less) of how this work applies to sex difference, gender biology, or women’s health research will be judged to select featured talks.

**Abstract**

Epidemiological research has uncovered multiple risk factors for COVID-19 severity, including sex, cardiometabolic status, and social determinants of health. Meanwhile, genetic studies have shown that specific genomic regions are associated with severe COVID-19. However, it is not clear whether genetic factors impact the relationship between these key risk factors and COVID-19 severity. We sought to understand the interactions between genetic variants and risk factors in order to shed light on COVID-19 biology and susceptible communities. We undertook a series of three genome-wide gene-environment interaction studies in the UK Biobank, while conducting both interaction effect tests and joint tests of genetic main and interaction effects. The “environmental” exposures included sex, cardiometabolic health (obesity and type 2 diabetes), and social determinants of health (as quantified by the multiple deprivation index), while the binary outcome was severe COVID-19, as defined by hospitalization or death due to COVID-19, while using the rest of the population as controls. We found four significant genomic regions that uncover some biological underpinnings of variable COVID-19 severity, two of which came from the sex interaction analysis. For example, one genome-wide significant variant (rs2268616), identified in the sex joint interaction and cardiometabolic interaction analyses, is found in an intron of the placental growth factor gene and has been previously linked to testosterone levels. Interestingly, other studies have found that SARS-CoV-2 can enter the testis and delay viral RNA clearance in males, possibly contributing to differential immune responses between sexes. While we did not find substantial evidence for genetic modification of the importance of risk factors (via the interaction test), our joint test results showed that incorporation of these risk factors, particularly sex, improved the detection of genetic loci impacting COVID-19 severity.

**Description**

Male sex is independently associated with worse COVID-19 outcomes and higher mortality. Sex-dimorphic genes and hormones, as well as differences in environmental factors between the sexes, maybe contribute to differential immune responses between sexes and mediate this association. Our work seeks to explore interactions between genetic variants and key COVID-19 risk factors, including sex, impacting the severity of COVID-19 outcomes. Exploring the interplay of genetics and sex can offer novel understanding of the underlying mechanisms impacting COVID-19 severity and add an important dimension to the current epidemiological literature on COVID-19.