**UKB COVID-19 GxE Analysis Plan**

Background

Epidemiological research has found multiple risk factors of COVID-19 severity, including sex, cardiometabolic status, and social determinants of health. Male sex was shown to be independently associated with higher mortality and worse outcomes of COVID-19 (Palaiodimos et al., 2020), and the risk of severe illness or death caused by COVID-19 was found to be both increased in males compared to females (Park et al., 2020). Obesity and T2D are also associated with increased COVID-19 susceptibility and severity. Obesity was specifically highlighted as potentially causal via MR methods, perhaps mediated through T2D (Leong et al., 2020). Results of a nationwide analysis in England showed that Type 1 and Type 2 diabetes were both independently associated with a significant increased odds of in-hospital death with COVID-19 (Barron 2020). Minority communities also have disproportionately worse outcomes of COVID-19, and may be predisposed to worse conditions due to environmental factors, limited healthcare access, and other societal factors (Tai et al., 2020). Complementing this set of prominent risk factors, genetic investigations, such as the Host Genetics Initiative, have started to uncover genetic underpinnings of COVID severity.

Preliminary results from analyses in the Manning Lab have suggested scientific directions to better understand the above risk factors and their interplay. Mendelian Randomization methods have indicated causality of obesity and COVID-19 severity, as well as significant genetic heterogeneity in testing sex stratified BMI and COVID-19 severity. Results from a preliminary UKB interaction analysis also found biologically-plausible loci showing suggestive interactions with T2D influencing COVID lethality. More in-depth interaction analysis leveraging additional known COVID-19 risk factors as exposures has the potential to uncover interactions that shed light on COVID-19 biology and inform the prediction of particularly susceptible individuals.

Objective

To conduct a genome-wide interaction study in the UK Biobank to investigate the interaction between genetic variants and each of sex, obesity, T2D, and social determinants of health in their impact on COVID-19 severity.

Hypothesis

Primary Hypothesis: There are genetic variants that modify the effect of known COVID-19 risk factors on COVID-19 severity (and vice versa).

Secondary Hypothesis: Incorporation of known COVID-19 risk factor interactions via a joint test can increase the power to uncover genetic loci associated with COVID-19 severity.

Dataset

* Population: Unrelated individuals in UKB
  + Multi-ancestry (European, West African, East Asian, and South Asian)
  + Sample sizes will depend on availability of phenotypes
* Genotypes: Largely rely on the processing already performed by the UKB group
  + Marker-level: Batch/plate/sex/array effect marker removal and HWE
  + Sample-level: High heterozygosity and >5% missingness
  + Subset to common variants (MAF > 0.01)
  + Genotypes available as .bgen files

Exposures of Interest

* Genetically-determined sex
* **Cardiometabolic diseases**
  + Obesity as measured by BMI
  + T2D (existing “prob\_poss” definition derived within the Florez lab UKB project)
* **Social determinants of health**
  + Multiple deprivation index, composed of metrics including:
    - Economic stability
    - Physical environment
    - Education

Outcomes

* COVID-19 severity defined as hospitalization
  + Definition based on Host Genetics Initiative “B2” Phenotype (Hospitalized COVID vs population)
* Secondary outcomes:
  + COVID-19 severity defined as intubation or mechanical ventilation
  + COVID-19 susceptibility determined by tests of RNA PCR, serologic testing, or clinician diagnosis by chart review or ICD-coding
  + Lethality (building off of Andrew’s preliminary UKB analysis of T2D and COVID-19)
  + Ordinal COVID-19 severity coding

Methods

* Interaction model
  + y (COVID-19 hospitalization) ~ g + exposure + g\*exposure + age + sex + 5 genetic PCs
  + Covariates: age, sex, 5 genetic PCs
* Statistical tests
  + Interaction test (primary; joint interaction test of multiple exposures for metabolic and SDH risk factors)
  + Joint test of genetic main and interaction effect (secondary)
  + Implement in GEM
  + Robust standard errors
  + Ancestry-stratified analyses (4 ancestries) + meta-analysis
* Obese and non-obese stratified analysis to test T2D exposure effect
* Analysis to be conducted on Terra

Roles and Responsibilities

* Social determinants of health definition - Beza and Joanna
* COVID-19 severity definition - Magda
  + Including phenotype pre-processing on Terra
* Post-processing and visualization of GWAS data - Joanna and Kenny
  + Use notebooks on Terra? Can Joanna get access?
* Running the GxE analyses - Mark O’Connor, Kenny

References

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