Genetic correlations between COVID-19 and a variety of traits and diseases

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The ongoing coronavirus disease (COVID-19) outbreak has posed an extraordinary threat to global public health. Patients with certain underlying medical conditions, such as obesity, hypertension, and diabetes are at increased risk for poor outcome in COVID-19.[1] Given the high genetic heritability of the aforementioned conditions, their shared genetic factors may play a crucial role in the severity of COVID-19. Indeed, a recent genome-wide association study (GWAS) of COVID-19 has reported two genomic loci associated with severe COVID-19, indicating a strong genetic influence on the severity of COVID-19.[2] Here, we analyzed GWAS results released by the COVID-19 Host Genetics Initiative,[3] the UK biobank, and the GWAS Catalog to explore the genetic overlap between COVID-19 and a broad spectrum of traits and diseases (Figure 1).

Summary statistics of selected COVID-19 GWAS (sample size >30,000 and percentage of Europeans >90%) were downloaded from COVID-19 Host Genetics Initiative, including A2_ALL (very severe respiratory confirmed COVID-19 against population), B2_ALL (hospitalized COVID-19 against population), B2_ALL_eur (hospitalized COVID-19 against population in Europeans), and C2_ALL_eur (COVID-19 against population in Europeans). GWAS summary statistics of selected diseases/traits were downloaded from the UK biobank and the GWAS Catalog.[4] Genetic correlation r_g between COVID-19 and interested diseases/traits were estimated by LD (linkage disequilibrium) score regression using GWAS summary statistics that overlap with HapMap3 SNPs as recommended. Pre-computed linkage disequilibrium scores for HapMap3 SNPs calculated based on European-ancestry individuals from the 1000 Genomes Project were used in the analysis (supplemental information).

We first investigated genetic correlations between COVID-19 and 1,555 diseases/traits from the analysis of UK biobank data by the Neale lab (http://www.nealelab.is/uk-biobank/) as described in Figure 1. Our results are consistent with the epidemiological observation that BMI is significantly associated with severe or hospitalized COVID-19 (A2_ALL, rg = 0.24, p = 3.35×10^{-6}; B2_ALL, rg = 0.39, p = 3.33×10^{-7}). COPD (chronic obstructive pulmonary disease), heart diseases, hypertension, diabetes, and smoking status exhibit substantial magnitude of genetic correlation with COVID-19, although statistical significance does not pass the strict threshold after adjustment for multiple testing (Table S1). Collectively, diseases of the

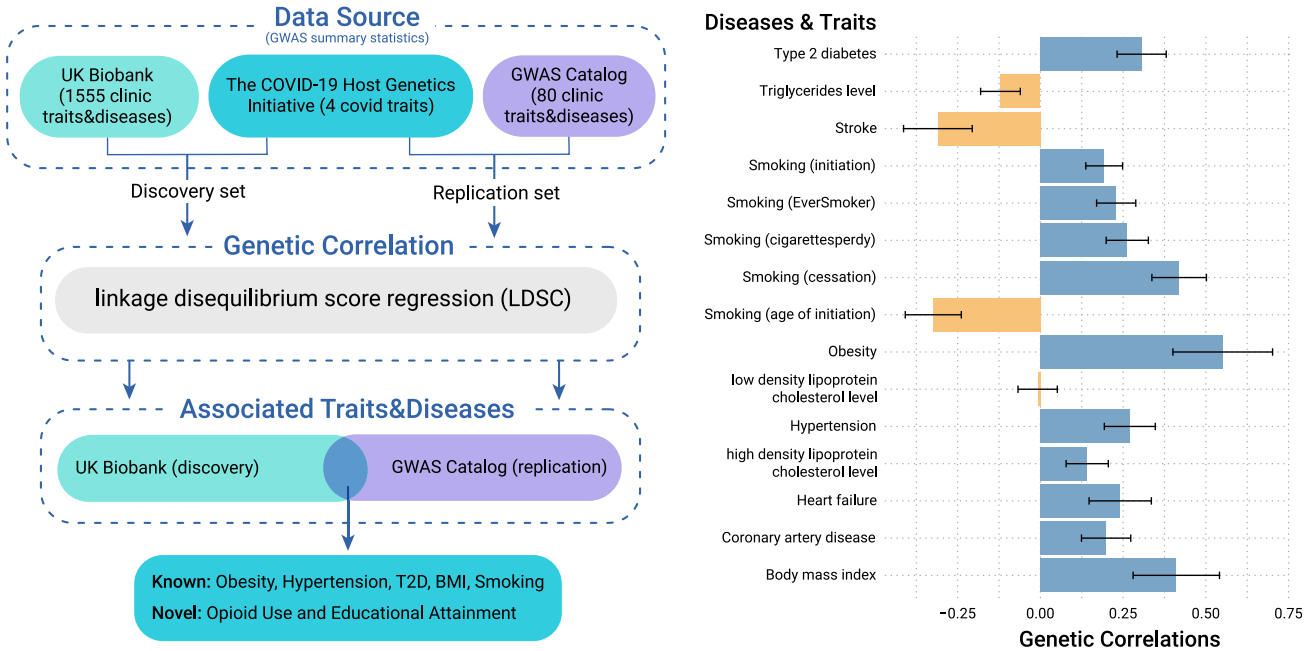

Figure 1. Flowchart of data preparation and analysis for COVID-19 and tested traits/diseases in this study More details of genetic correlation results are provided in https://roarchang.shinyapps.io/COV19_GC/.

circulatory system, diseases of the digestive system, and diseases of the musculoskeletal system and connective tissue are significantly associated with severe or hospitalized COVID-19 (Table S1). In agreement with this, a number of medication-taking traits linked to obesity, diabetes, hypertension, and digestion display modest correlation with COVID-19 (Table S1). Tramadol, an opioid pain medication, is significantly correlated with hospitalized COVID-19 (B2_ALL, rg = 0.65, p = 1.26×10^{-5}). Interestingly, our results indicated a significant negative correlation between severe or hospitalized COVID-19 and educational attainment-related traits, including college or university degree (A2_ALL, rg = −0.24, p = 8.51×10^{-7}; B2_ALL, rg = −0.32, p = 1.78×10^{-6}) and fluid intelligence score (A2_ALL, rg = −0.25, p = 2.40×10^{-5}; B2_ALL, rg = −0.26, p = 7.66×10^{-5}). Hospitalized COVID-19 (B2_ALL, rg = 0.73, p = 8.60×10^{-6}) is also significantly correlated with panic attacks.

We next estimated genetic correlations between COVID-19 and 80 diseases/traits from the GWAS Catalog[4] (Figure 1). Consistently, hypertension, type 2 diabetes, and obesity are significantly associated with severe or hospitalized COVID-19 (Table S1). Coronary artery disease, heart failure, and BMI are also modestly associated with severe COVID-19. Likewise, medication-taking traits related to obesity, diabetes, hypertension, and digestion are modestly associated with COVID-19, such as drugs for diabetes and antihypertensives (Table S1). Significant correlations are also found between hospitalized COVID-19 and drugs for peptic ulcer and gastro-esophageal reflux disease (B2_ALL, rg = 0.34, p = 3.01×10^{-5}; B2_ALL_eur, rg = 0.28, p = 0.0006), diuretic use and very severe respiratory confirmed COVID-19 (A2_ALL, rg = 0.25, p = 0.0002), opioids and severe or hospitalized COVID-19 (A2_ALL, rg = 0.30, p = 5.59×10^{-5}; B2_ALL, rg = 0.44, p = 4.78×10^{-7}; B2_ALL_eur, rg = 0.38, p = 0.0002). Consistent with the findings from the UK biobank data, a strong negative genetic correlation between educational attainment and severe or hospitalized COVID-19 (A2_ALL, rg = −0.33, p = 1.90×10^{-9}; B2_ALL, rg = −0.41, p = 1.82×10^{-8}; B2_ALL_eur, rg = −0.35, p = 2.07×10^{-6}) is observed. Further analyses of brain function and personality traits show that COVID-19 is significantly correlated with cognitive performance and verbal-numerical reasoning, but not memory performance, reaction time, or neuroticism (Table S1). In addition, very severe respiratory confirmed COVID-19 (A2_ALL, rg = −0.37, p = 0.0006) is significantly correlated with systemic lupus erythematosus.

Although the genetic correlation alone does not explain the causal mechanism that might link two diseases, it provides evidence of potential causal relationships among genetic diseases, and potentially lead to new disease interventions. Here, our genetic correlation results between COVID-19 and a variety of traits and diseases confirm medical conditions and risk factors reported from epidemiological studies, such as hypertension, type 2 diabetes, and obesity. However, as far as we are aware, the association between opioids and COVID-19 has not previously been reported using epidemiological data. As side effects associated with chronic opioid use at high doses may affect the immune system and increase the risk of pneumonia, there is an urgent need to evaluate the relationship between COVID-19 severity and opioid use by epidemiological studies.[5] Also, patients using chronic opioids may be considered a vulnerable group for careful monitoring. In addition, our results suggest that immune pathways involved in systemic lupus erythematosus may also play an important role in the severity of COVID-19. Finally, the observed negative correlation between COVID-19 severity and educational attainment reflects an indirect link mediated by environment or human behavior. For example, patients with different educational levels may differ in diet choices (BMI) or smoking status, and their occupations and/or living conditions may put them at higher risk of exposure to the virus. This study provides novel information on underlying conditions that might increase the risk of severe COVID-19 illness. Added epidemiological studies are warranted to further evaluate these findings.

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AUTHOR CONTRIBUTIONS

H.H. and X.C. designed the research and wrote the paper. X.C. and Y.L. performed the analysis. K.N., H.Q., and Y.L. collected the data and revised the paper. J.G., P.M.A.S., and H.H. supervised this study. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interest.

SUPPLEMENTAL INFORMATION

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