GENETIC IMPACT OF COVID-19 INFECTION AND SEVERITY ON ALZHEIMER’S DISEASE

PURPOSE/BACKGROUND

The COVID-19 pandemic, caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has impacted many facets of our life, including neurodegenerative disorders such as Alzheimer’s disease (AD). Notably, AD has emerged as a key comorbidity of COVID-19 infection, and the aging population is highly susceptible to COVID-19 infection with higher death rate. Leveraging large publicly available large genome-wide association study (GWAS) data, this study examined the overlapping genetic liability between AD and COVID-19 disease. Our goal is to better understand the genetic impact of COVID-19 on AD and discover new strategies for better prevention and treatments.

MATERIALS & METHODS

The COVID-19 GWASs from the European population (HGI7_Eur released on 04/08/2022) were downloaded from the COVID-19 Host Genetics Initiative website. Three categories of COVID-19 phenotypes vs. regular population were included in this study: 1) critically ill cases of COVID-19 (A2, case/ctrl = 13,769/1,072,442); 2) hospitalization due to moderate or severe COVID-19 (B2, case/ctrl = 32,519/2,062,805); 3) COVID-19 susceptibility with all cases (C2, case/ctrl = 2,475,240/12,597,856). AD genotyping datasets included the NIA/LOAD cohort and the Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer’s Disease (GenADA) Study (total case/ctrl = 3,119/3,023). In this study, we conducted polygenic risk score (PRS) analyses (PRSice v2.3.5) at multiple GWAS P-value thresholds ($P_T$: $5 \times 10^{-8}$, $1 \times 10^{-5}$, $1 \times 10^{-3}$, $1 \times 10^{-1}$, 1.0) and “best-fit” GWAS $P_T$ ranging from $5 \times 10^{-8}$ to 1 with an incremental interval of 0.00005. Significant correlation was determined when the associated $P$-val $< 0.017$ (0.05/3) with multiple test correction. We also rescaled PRSs [-1,1] and conducted logistic regression analyses to compare the odds ratios and re-evaluate the association with adjustment for other covariates, such as age, sex, and $APOE$ genotyping (rs429358 and rs7412).

RESULTS

We found significant positive correlations between AD diagnosis and genetic risk for different phenotypes of COVID-19. As seen in Table 1, AD was significantly associated with COVID-19 infection ($P = 7.43E-05$, coeff. = 1928.98), critical COVID-19 ($P = 0.00162$, coeff. = 274.59), and hospitalization ($P = 0.01523$, coeff. = 112.47). Adjusted for age, sex, and $APOE$ genotyping, AD was still significantly associated with COVID-19 infection [$P$-adj. = $1.29E-06$, OR(CI95%)-adj. = 1.878(1.457-2.428)], critical COVID-19 [$P$-adj. = $0.00056$, OR(CI95%)-adj. = 1.496(1.191-1.882)], and marginal association with hospitalization [$P$-adj. = $0.04172$, OR(CI95%)-adj. = 1.265(1.009-1.586)]. Multiple positive associations were also found as significant between AD diagnosis and genetic risk for COVID-19 infection at different GWAS $P_T$ (Fig. 1.)

<table>
<thead>
<tr>
<th>phenotypes</th>
<th>Case</th>
<th>Ctrl</th>
<th>total</th>
<th>$P_T$</th>
<th>$R^2$</th>
<th>Coeff.</th>
<th>SE</th>
<th>SNP#</th>
<th>OR (CI 95%)</th>
<th>$P$-val</th>
<th>OR(CI95%)-adj.</th>
<th>$P$-adj.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Cond (A2)</td>
<td>13769</td>
<td>1072442</td>
<td>1086211</td>
<td>0.0039</td>
<td>0.002</td>
<td>274.6</td>
<td>87.1</td>
<td>8553</td>
<td>1.396(1.134-1.716)</td>
<td>0.00162</td>
<td>1.496(1.191-1.882)</td>
<td>0.00056</td>
</tr>
<tr>
<td>Hospitalization (B2)</td>
<td>32519</td>
<td>2062805</td>
<td>2096324</td>
<td>0.0003</td>
<td>0.001</td>
<td>112.5</td>
<td>46.3</td>
<td>1275</td>
<td>1.288(1.050-1.581)</td>
<td>0.01523</td>
<td>1.265(1.009-1.586)</td>
<td>0.04172</td>
</tr>
<tr>
<td>Infection (C2)</td>
<td>122616</td>
<td>2475240</td>
<td>2597856</td>
<td>0.0432</td>
<td>0.003</td>
<td>1929.0</td>
<td>486.8</td>
<td>59061</td>
<td>1.596(1.268-2.013)</td>
<td>7.43E-05</td>
<td>1.878(1.457-2.428)</td>
<td>1.29E-06</td>
</tr>
</tbody>
</table>

Note: Case, control (Ctrl), and total are the sample size included in the most recent COVID-19 GWASs from HGI7 for European population; $P_T$-value threshold from GWAS $P$-value; $R^2$: how much variance explained by the model; Coeff.: coefficient; SE: standard error; SNP#: how many number of SNPs are included in the “best-fit” model; OR: odds ratio from logistic regression analyses with rescaled PRSs [-1,1] without any adjustment; CI: confident interval without any adjustment; $P$-val: association $P$-value between PRSs and AD diagnosis without any adjustment; $P$-adj.: association $P$-value between PRSs and AD diagnosis with adjustment for age, sex, and $APOE$ genotyping (rs429358 and rs7412); OR(CI95%)-adj.: odds ratio and 95% confident interval with adjustment for age, sex, and $APOE$ genotyping (rs429358 and rs7412). $P$-val in bold represents statistically significant.
Using the polygenic risk score approach, we identify a strong genetic correlation between AD diagnosis and genetic risks for COVID-19 (infection, critical illness, and hospitalization), suggesting that COVID-19 patients from different clinical manifests all have higher genetic risk to develop AD. With the ongoing outbreak of COVID-19 and the high vulnerability of AD from COVID-19 infection, our findings highlight the importance offering preventative measures to patients with COVID-19 and provide a genetic base for understanding the neurological impact of COVID-19.

**DISCUSSION/CONCLUSION**

Fig. 1. Bar plot showing significant associations between AD and PRSs for COVID-19 infection (C2) at multiple $P_T$ ranging from 0.001 to 1 with the best $P_T$ at 0.0432. The highest bar indicates the "best-fit" PRS associated with AD.

X-axis: $P$ value threshold. Y-axis: PRS model fit $R^2$ indicates how much variance explained by the model. Color indication gradient is based on a -log model $P$-value.