Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

A genome-wide cross-trait analysis highlights the shared genetic structure between COVID-19 and Alzheimer's disease

Dear Editor,

We read with interest the recently published research in *Journal of Infection* by Yang et al. who reported the higher mortality of COVID-19 patients with dementia compared with COVID-19 patients without dementia (effect estimate = 1.84, 95% CI: 1.57–2.16).[1] Meanwhile, patients recovering from COVID-19 had a more severe burden of cognitive impairment, suggesting the potential risk of Alzheimer's disease.[2] Although growing evidences indicate the potential genetic overlap between Alzheimer's disease and COVID-19, the genetic association degree and the shared genetic structure region between the two diseases remain unknown.[3] In this study, we aim to clarify the following three questions: (I) Does the genetic association exist between COVID-19 and Alzheimer's disease? (II) Where is the shared genetic region between COVID-19 and Alzheimer's disease? (III) Is there a causal relationship between COVID-19 and Alzheimer's disease?

In order to answer these questions, we obtained two large-scale genome-wide association studies (GWAS) summary statistics of Alzheimer's disease and COVID-19, respectively from International Genomics of Alzheimer's Project (IGAP) and COVID-19 Host Genetics Initiative.[4,5] All the participants were of European descent. In stage 1, we evaluated genetic correlation between Alzheimer's disease and COVID-19 using linkage disequilibrium score (LDSC) regression analysis.[6] From an overall point of view, the genetic association seemed to have only suggestive significance (r_g = 0.1048, P = 0.0782). In stage 2, We divided the gene components into 1703 LD-independent segments and calculated local genetic correlation of each segment, respectively using HESS (heritability estimation from summary statistics)[1]. Chr19:44,744,108–46,102,697, containing several known Alzheimer's disease susceptibility loci, was the shared genetic region of Alzheimer's disease and COVID-19 (P = 4.38E-04). In chr19:44,744,108–46,102,697, *APOE* and *APOC1* have been proven to be enriched in certain immune cells or tissues of COVID-19 patients and mediate the infection of SARS-CoV2 in neurons and astrocytes.[7,8] In stage 3, we performed a bidirectional two-sample Mendelian randomization (MR) analysis to reveal the causality between Alzheimer's disease and COVID-19.[9] When Alzheimer's disease was used as exposure and COVID-19 as outcome, 18 genetic variants were used as instrumental variables to carry out MR analysis. Inverse variance weighted (IVW) method showed a higher risk of COVID-19 for Alzheimer's disease patients (OR = 1.06, 95% CI: 1.00–1.12, P = 0.042) (Table 1). However, reverse MR found no evidence that COVID-19 led to Alzheimer's disease (P = 0.202).

Table 1
Five main methods to perform MR analysis between Alzheimer's disease and COVID-19.

Method[b]	N_{SNP}	b[a]	se	*P*	OR
MR Egger	18	0.0665	0.029	0.038	1.069 (1.01–1.13)
Weighted median	18	0.0582	0.029	**0.042**	1.06 (1.00–1.12)
Inverse variance weighted	18	0.0174	0.023	0.459	1.02 (0.97–1.07)
Simple mode	18	0.0123	0.061	0.843	1.01 (0.90–1.14)
Weighted mode	18	0.0595	0.027	**0.039**	1.06 (1.01–1.12)

[a] b→Beta, se→SE
[b] Method→MR methods

In conclusion, we supported the potential genetic association between Alzheimer's disease and COVID-19, which was mainly reflected in chr19:44,744,108–46,102,697 region. *APOE, APOC1* and other related genes might be an important reason why patients with Alzheimer's disease were more susceptible to COVID-19. Although Alzheimer's disease might increase the risk of COVID-19, the causality was not clear enough (Table 1). We recommend that our views should be further validated in future clinical and observational studies.

Declaration of Competing Interest

All the authors declare no conflicts of interest.

Acknowledgment

This work was supported by the National Key Research and Development Program of China (2017YFC1201201, 2018YFC0910504 and 2017YFC0907503), the Natural Science Foundation of China (61801147 and 82003553) and Heilongjiang Postdoctoral Science Foundation (LBH-Z6064).

We thank International Genomics of Alzheimer's Project (IGAP) and COVID-19 Host Genetics Initiative for providing GWAS summary statistics.

Reference

1. Yang H, Liang X, Hou H, Xu J, Shi L, Wang Y. The association of dementia with COVID-19 mortality: evidence based on adjusted effect estimates. *J Infect* 2021;**82**(5):e6–e10 MayPubMed PMID: 33582205. Pubmed Central PMCID: PMC7879026. Epub 2021/02/15.
2. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021;**594**(7862):259–64 JunPubMed PMID: 33887749. Epub 2021/04/23.
3. Lim KH, Yang S, Kim SH, Joo JY. Elevation of ACE2 as a SARS-CoV-2 entry receptor gene expression in Alzheimer's disease. *J Infect* 2020;**81**(3) Sepe33-e4. PubMed PMID: 32619698. Pubmed Central PMCID: PMC7834154. Epub 2020/07/04.
4. Initiative C.H.G. Mapping the human genetic architecture of COVID-19. *Nature* 2021 Jul 8PubMed PMID: 34237774. Epub 2021/07/09, https://www.nature.com/articles/s41586-021-03767-x.

[1] Add reference: Shi HWB, Mancuso N, Spendlove S, Pasaniuc B. Local Genetic Correlation Gives Insights into the Shared Genetic Architecture of Complex Traits. Am J Hum Genet. 2017 Nov 2;101(5):737-51.

https://doi.org/10.1016/j.jinf.2021.08.038

5. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates abeta, tau, immunity and lipid processing. *Nat Genet* 2019;**51**(3):414–30 MarPubMed PMID: 30820047. Pubmed Central PMCID: PMC6463297. Epub 2019/03/02.
6. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, et al. An atlas of genetic correlations across human diseases and traits. *Nat Genet* 2015;**47**(11):1236–41 NovPubMed PMID: 26414676. Pubmed Central PMCID: PMC4797329. Epub 2015/09/29.
7. Shaath H, Vishnubalaji R, Elkord E, Alajez NM. Single-cell transcriptome analysis highlights a role for neutrophils and inflammatory macrophages in the pathogenesis of severe COVID-19. *Cells* 2020;**9**(11):2374 Oct 29PubMed PMID: 33138195. Pubmed Central PMCID: PMC7693119. Epub 2020/11/04.
8. Wang C, Zhang M, Garcia G, Tian E, Cui Q, Chen X, et al. ApoE-isoform-dependent SARS-CoV-2 neurotropism and cellular response. *Cell Stem Cell* 2021;**28**(2):331–42 Feb 4e5. PubMed PMID: 33450186. Pubmed Central PMCID: PMC7832490. Epub 2021/01/16.
9. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-base platform supports systematic causal inference across the human phenome. *Elife* 2018;**7**:e34408 May 30PubMed PMID: 29846171. Pubmed Central PMCID: PMC5976434. Epub 2018/05/31.

Shizheng Qiu, Yang Hu*
School of Life Science and Technology, Harbin Institute of Technology, No. 2 Yikuang Street, Nangang District, Harbin 150001, China

Liang Cheng*
College of Bioinformatics Science and Technology, Harbin Medical University, No. 157, Health Road, Nangang District, Harbin 150076, China

*Corresponding authors.
E-mail addresses: huyang@hit.edu.cn (Y. Hu), liangcheng@hrbmu.edu.cn (L. Cheng)