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.

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Letter to the Editor

Elevation of *ACE2* as a SARS-CoV-2 entry receptor gene expression in Alzheimer's disease

Dear Editors,

We read with a recent study by Liu and colleagues, published in the Journal of Infection, described the mortality of elderly patients with Covid-19 compared to young and middle-age patients.[1] In addition, we also read an interest article by Fu and colleagues in this journal, the SARS-CoV-2 pandemic that showed high mortality in older adults who have chronic comorbidities such as chronic obstructive pulmonary disease (COPD).[2] Considering the high mortality rate and pandemic status of COVID-19, development of effective therapeutics is an urgent issue that requires the identification of quality pathogen. Genomic characterization recently revealed that angiotensin-converting enzyme 2 (ACE2) is a SARS-CoV-2 binding protein for cell entry, and control of ACE2 is a potential therapeutic target to reduce SARS-CoV-2 transmission.[3] Thus, there is an urgent need for studies of genomic expression of *Ace2* gene in elderly COVID-19 patients. The hope is that such studies will allow researchers to decrease the mortality rate and prevent new SARS-CoV-2 infections.

A main risk factor for the development of neurodegenerative diseases (NDs) is aging, Alzheimer's disease (AD) is the most common ND in older adults.[4] The main cause of AD is the aggregation of Aβ peptide in brain tissue; several related symptoms, such as hippocampal sclerosis, are frequently detected.[5] Moreover, a recent study suggested that AD patients who have comorbidities such as COPD showed increased cognitive decline.[6] Given that AD patients have particularly susceptible respiratory systems, we hypothesized that high ACE2 expression may be related to higher mortality in AD patients. We thus queried RNA-seq data and performed a genome-wide association study (GWAS) for *Ace* genes in an AD model (Fig. 1A). Expression analysis of the increase in *Ace* genes in the AD mouse model showed dominant expression of the *Ace2* gene in brain tissue (Fig. 1B). However, unlike *Ace2, Ace1* gene expression did not differ in healthy vs. diseased brain tissue (Fig. 1B). We also analyzed *Ace2* gene expression levels in blood and found no significant differences (Fig. 1B). *Ace1* gene expression showed a slightly decreased tendency in AD brain tissue; on the other hand, we observed that *Ace1* gene expression was significantly increased in blood (Fig. 1B). This means that *Ace1*gene may be a specific biomarker for AD diagnosis. Having observed changes in *Ace* gene expression levels in AD model brain and blood, we next analyzed human *Ace* gene expression profiles in the brain tissue and peripheral blood mononuclear cells (PBMCs) of human AD patients. Gene difference analysis showed that *Ace2* gene expression levels gradually elevated in incipient (135%), moderate (148%), and severe patients (164%) groups vs. healthy groups, however *Ace1* gene expression levels decreased by 32% in incipient patients, and then return to normal levels in moderate and severe patients groups (111% and 116%, respectively) (Fig. 1C). On the other hand, *Ace1* gene was expressed at a level of 39% and *Ace2* gene was expressed at a level of 69% compared to the normal groups. (Fig. 1D). These analyzes strongly indicate that *Ace2* gene expression is elevated in AD brain tissue, which may be a risk factor for Covid-19 transmission in AD patients. Advancements in Covid-19 host genomics research are currently required for development of medicine or therapeutics.[7] Here, we report on genetic risk factors for transmission of SARS-CoV-2 in AD patients using GWAS. Emerging analyses may link these findings to prevention or therapeutics for SARS-CoV2. We found that expression of the *Ace2* gene, which codes for a SARS-Cov-2-binding protein, was increased in AD patient brain. Interestingly, ACE inhibitors have recently been suggested as treatments for NDs.[8] Therefore, ACE inhibitors may treat both NDs and Covid-19. Collectively, our results suggest that high ACE2 expression may be a risk factor for Covid-19 transmission in AD patients. Careful diagnosis and healthcare provisions are needed to address this issue therapeutically.

Declaration of Competing Interest

All financial and non-financial competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.06.072.

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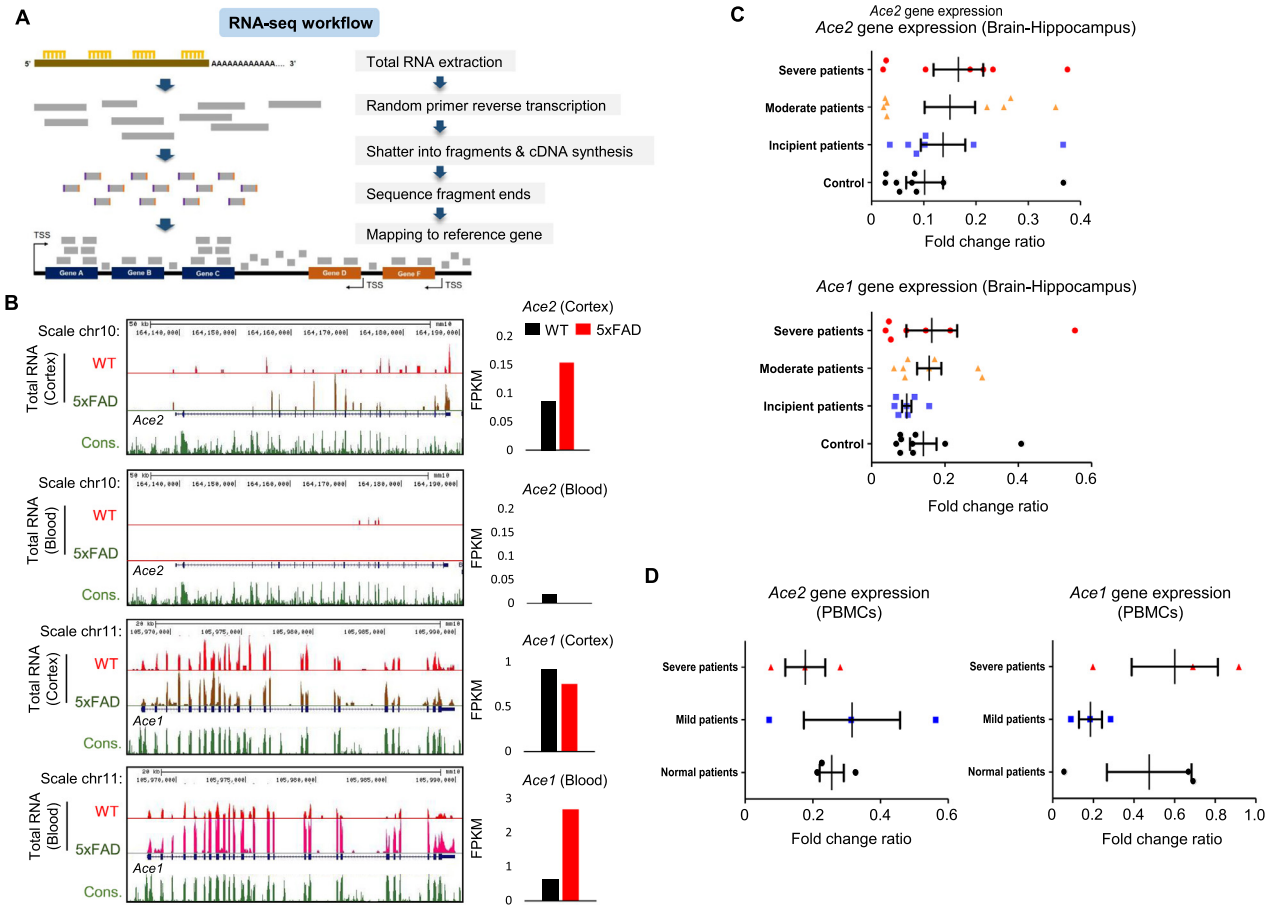

Fig. 1. *Ace2* gene expression profiling in AD patient brain. (**A**) Gene expression is quantified by total RNA-seq. Extracted total RNAs were synthesized to cDNA using random primers. Gene expression profiling was based on Agilent GeneSpring analysis; image was generated by the FASTQ illumine package bcl2faseq. Single- or paired-end reads were calculated from next generation sequencing (NGS). (**B**) Visualization of *Ace1* and *Ace2* gene expression in the UCSC genome browser. Representative UCSC genome browser tracks of *Ace1* and *Ace2* are shown for cortex and whole blood. Total RNA-seq covered for whole *Ace1* and *Ace2* gene expression region and mapping each sequencing reads. *Ace2* fragments per kb per million reads (FPKM) values are significantly increased in 5xFAD cortex. *Ace1* FPKM values are increased in AD model blood. There was no significant change of *Ace1* in 5xFAD cortex. *Ace2* showed very small amount of gene expression both WT and 5xFAD. The FPKM values for each gene were calculated with the Cufflinks package. (**C**) Analysis of *Ace1* and *Ace2* gene expression profile from human brain microarray dataset in AD patients. Gene expression analysis in hippocampus showed that *Ace2* gene expression levels are elevated in the severe patient group compared to healthy group (135%, 148%, 164%, respectively). On the other hand, *Ace1* gene expression levels decreased by 32% in incipient patients, and then return to normal levels in moderate and severe patient groups (111% and 116%, respectively). Control group $n = 9$, incipient group $n = 7$, moderate group $n = 8$, severe group $n = 7$. (**D**) Analysis of *Ace1* and *Ace2* gene expression profile from human PBMCs microarray dataset in AD patients. Gene expression analysis result in human PBMCs showed that *Ace1* gene was expressed at a level of 39% compared to the normal groups, whereas *Ace2* gene was expressed at a level of 69% compared to the normal groups. Normal patients group $n = 3$, Mild patients group $n = 3$, Severe patients group $n = 3$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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