



Identifying New COVID-19 Receptor Neuropilin-1 in Severe Alzheimer's Disease Patients Group Brain Using Genome-Wide Association Study Approach

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Recent preclinical studies show that Neuropilin-1 (NRP1), which is a transmembrane protein with roles in neuronal development, axonal outgrowth, and angiogenesis, also plays a role in the infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Thus, we hypothesize that NRP1 may be upregulated in Alzheimer's disease (AD) patients and that a correlation between AD and SARS-CoV-2 NRP1-mediated infectivity may exist as angiotensin converting enzyme 2 (ACE2). We used an AD mouse model that mimics AD and performed high-throughput total RNA-seq with brain tissue and whole blood. For quantification of NRP1 in AD, brain tissues and blood were subjected to Western blotting and real-time quantitative PCR (RT-qPCR) analysis. *In silico* analysis for NRP1 expression in AD patients has been performed on human hippocampus data sets. Many cases of severe symptoms of COVID-19 are concentrated in an elderly group with complications such as diabetes, degenerative disease, and brain disorders. Total RNA-seq analysis showed that the *Nrp1* gene was commonly overexpressed in the AD model. Similar to ACE2, the NRP1 protein is also strongly expressed in AD brain tissues. Interestingly, *in silico* analysis revealed that the level of expression for NRP1 was distinct at age and AD progression. Given that NRP1 is highly expressed in AD, it is important to understand and predict that NRP1 may be a risk factor for SARS-CoV-2 infection in AD patients. This supports the development of potential therapeutic drugs to reduce SARS-CoV-2 transmission.

Keywords: SARS-CoV-2, Neuropilin-1, Alzheimer's disease, genome-wide association study (GWAS), gene expression

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is being evaluated as a third-high-risk contagious infection (Hu et al., 2020). People are still highly vulnerable to the ongoing and life-threatening COVID-19 pandemic, as FDA-authorized vaccines or beneficial treatments remain unavailable (Singh et al., 2020). The risk of severe complications that are eventually

associated with high mortality is indicated in older people (Carstensen et al., 2020). Moreover, a bidirectional interrelation between neurological complications and COVID-19 is extensively reported (Verkhatsky et al., 2020).

Age-dependent vulnerability to SARS-CoV-2 has been associated with concomitant symptomatic infections (Liu et al., 2020; Wu et al., 2020). Alzheimer's disease (AD) is a highly destructive neurodegenerative disorder that mostly affects the elderly and is characterized by a progressive cognitive decline (Masters et al., 2015). Although various hypotheses have been proposed to explain its multifactorial properties (Liu et al., 2019), the exact mechanism and related features of AD remain obscure. An analysis of 627 patients suggests that AD is a risk factor for SARS-CoV-2 infection (Bianchetti et al., 2020).

Angiotensin converting enzyme 2 (ACE2) is required for SARS-CoV-2 infection. Recently, it is reported that the *Ace2* gene and protein expression are elevated in AD patients compared with in normal elderly individuals (Ding et al., 2020; Lim et al., 2020; Rahman et al., 2020). Consistent with these results, an increase in ACE2 expression results in an increased susceptibility to SARS-CoV-2 infection in elderly patients with AD. Furthermore, a recent study suggests that the transmembrane protein Neuropilin-1 (NRP1) also plays a role in SARS-CoV-2 infection (Daly et al., 2020; Mayi et al., 2021). Biochemical experiments and X-ray crystallography show that NRP1 strongly interacts with a polybasic sequence on the spike protein of SARS-CoV-2, which fits the C-end rule region (CendR) required for NRP1-peptide interaction (Daly et al., 2020; Song et al., 2020). NRP1 depletion with RNAi targeting *Nrp1* mRNA inhibits the binding of the SARS-CoV-2 spike protein to NRP1 and, consequently, decreases the rate of viral infection (Daly et al., 2020; Song et al., 2020). In addition, a monoclonal antibody against the b1b2 domain of NRP1 reduces the infectivity of SARS-CoV-2 lentiviral pseudo-particles (Cantuti-Castelvetri et al., 2020). NRP1 is a neuronal receptor associated with the regulation of neurite outgrowth through the binding of vascular endothelial growth factor (VEGF) (Abdullah et al., 2020). When NRP1 is activated by CendR, which is a peptide R/KXXR/K motif contained within C-terminal domains, it enables cells to internalize ligands, such as viruses, containing the motif (Teesalu et al., 2009). Furthermore, NRP1 is expressed in the central nervous system, including the brain olfactory-related regions in which SARS-CoV-2 entry may occur, thereby facilitating COVID-19 infection (Davies et al., 2020).

Thus, we hypothesize that, in addition to ACE2, NRP1 expression might be upregulated in the brains of elderly AD patients. In this study, molecular characterization via high-throughput analysis and biochemical assays reveals that NRP1 is highly expressed in AD, which suggests that NRP1 may be a potential genetic therapy target in AD patients with COVID-19.

MATERIALS AND METHODS

Animals

Five × FAD transgenic mice were purchased from the Jackson Laboratory. All animal experiments performed in this study were

reviewed and approved by the IACUC committee at the Korea Brain Research Institute (IACUC-20-00018).

Total RNA Sequencing and Human *in silico* Analysis

The data analysis of total RNA-seq from the mouse cortex was performed as previously described in Lim and Joo (2020). Briefly, the brain was extracted from 6-month-old wild-type (WT) and 5×FAD mice and cortex isolated to prepare the pure RNA and total RNA-seq library. RNA-seq libraries were prepared using the TruSeq Stranded Total RNA LT Sample Prep Kit (Illumina Sample Preparation Guide) from isolated mRNA. To profile the insert length of libraries, we used the Agilent 2100 Bioanalyzer, and constructed libraries were sequenced from HiSeqTM4000 platform (Illumina, United States). Then, converted nucleotide sequences using HiSeqTM4000 were sorted and the dirty reads filtered from the raw reads. RNA-seq data was accessible using Gene Expression Omnibus (GEO) accession number GSE147792. *In silico* data analysis was performed using the Affymetrix Human Genome U133 Plus 2.0 Array (Lim et al., 2020). The GSE1297 data sets were derived from human hippocampus and GSE4226 data sets were derived from human peripheral blood mononuclear cells (PBMCs) in normal and AD patients.

RNA Isolation

Total RNA isolation was performed with the mouse cortex according to TRIzol using the commercial protocol. First, phenol-based TRIzol (Invitrogen) is added in the cortex tissue tube for homogenizing. Then, it is separated into three phases by chloroform for the collect only RNA dissolved aqueous phase except the DNA and protein precipitated phases. An equal volume of isopropanol was used to precipitate RNA. After centrifugation, supernatant was discarded, and it was washed with prechilled 75% ethanol once. RNA was dehydrated and crystalized without organic compound contamination and eluted with nuclease-free water. RNA was then denatured in the 65°C heat block for 10 min. The procedure was performed without RNase contamination.

Complementary DNA Synthesis

Isolated total RNA was synthesized into complementary DNA (cDNA) following the manufacturer's protocol of High-Capacity cDNA Reverse Transcription Kits (Applied Biosystems). Template RNA (2 µg) was prepared to synthesize a single reaction, and reverse transcription kit components were premixed. The premixture contains 10 × RT buffer, 25 × dNTP mix (4 mM), 10 × RT Random Primers, MultiScribe Reverse Transcriptase (50 U), RNase inhibitor, and nuclease-free water for adjusting the total volume for the reaction. Gently mixed template RNA and an equal volume of premixture was placed in the thermal cycler. The condition for reverse transcription was suggested as optimized temperature and time: 25°C for 10 min, 37°C for 120 min, and 85°C for 5 min.

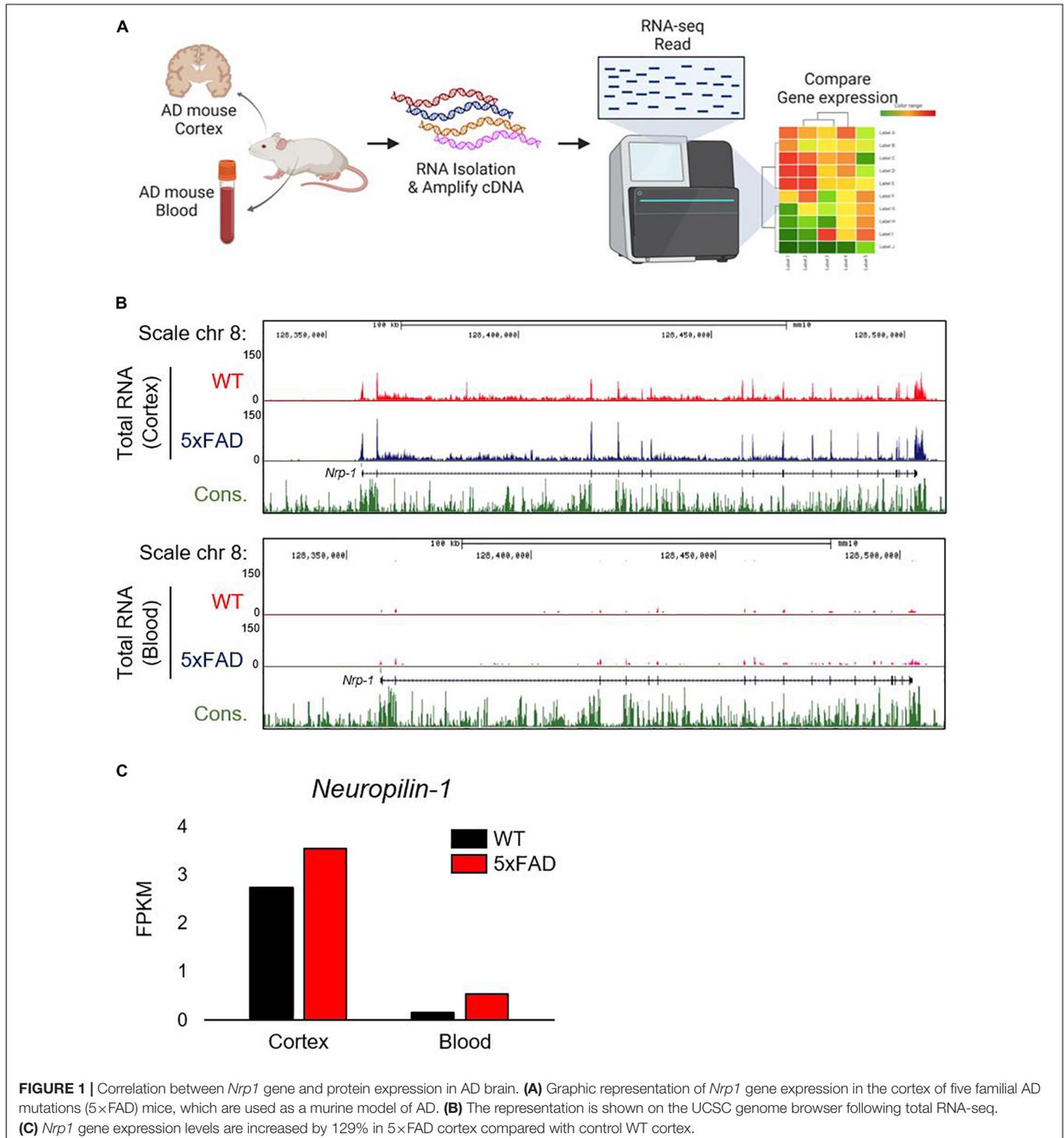
Real-Time Quantitative PCR

Real-time quantitative PCR (RT-qPCR) was performed according to commercial protocol using SYBR Green PCR Master Mix (Applied Biosystems). Primers employed were *Nrp1* forward, 5' CCTCACATTGGGCGTTATTG 3', reverse, 5' CACTGTAGTTGGCTGAGAAAC 3'; *Gapdh* forward, 5' AGGTCGGTGTGAACGGATTT 3', reverse, 5'

TGTAGACCATGTAGTTGAGG 3'. Each reaction contains SYBR Green PCR Master Mix, Template cDNA, and forward and reverse primer and is adjusted with nuclease-free water.

Western Blot

Protein was extracted from the mouse cortex and mixed with sample buffer (5% 2-mercaptoethanol) and boiled at 100°C for



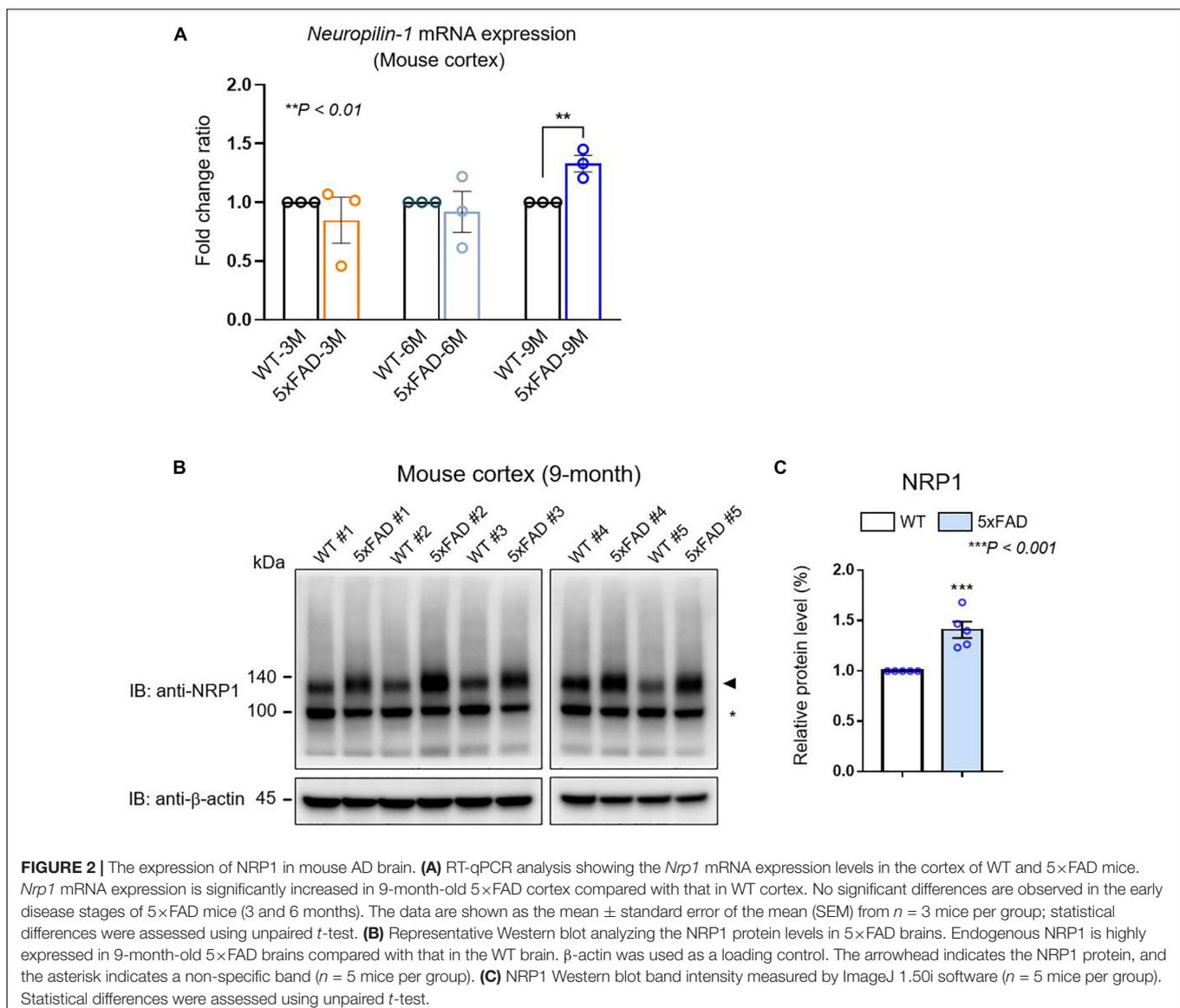
denaturation. Protein samples were loaded on 4–15% gradient gel (Bio-Rad) to separate by size through the vertical SDS-PAGE system. Antibodies used for immune-blot analysis were anti-Neuropilin-1 (abcam, 1:1000) and anti- β -actin (BETHYL, 1:10000). Images were acquired by ChemiDoc MP imaging system (Bio-Rad).

RESULTS

High-Throughput Analysis of *Nrp1* Expression in Alzheimer's Disease

Given that the gene expression of ACE2 is upregulated in the brains of patients with AD and may be associated with the mortality rate from COVID-19 in the elderly (Fu et al., 2020; Lim et al., 2020), we hypothesize that NRP1, which codes for a newly recognized SARS-CoV-2 spike receptor, may be also

increased in AD patients. To assess *Nrp1* gene expression in AD, we first used a murine model that mimics AD and performed total RNA-seq using mouse brain tissue and whole blood. Total RNA-seq was analyzed by the HiSeqTM4000 platform (Illumina, United States) (Figure 1A). We applied the *Nrp1* gene expression level in the brain and blood from AD and WT and then mapped the sequencing reads (Figure 1B). The track of *Nrp1* gene was displayed with University of California, Santa Cruz (USCS) genome browser (Figure 1B). Interestingly, total RNA-seq analysis revealed upregulation of *Nrp1* gene expression in the brain of the AD model compared to WT (Figure 1B), and *Nrp1* fragments per kb per million reads values are increased in the AD model brain as well (Figure 1C). Although *Nrp1* gene expression was increased by 319% in AD blood compared with WT blood, the endogenous expression levels of *Nrp1* in the blood were significantly lower than those in the brain (Figures 1B,C). Collectively, our total RNA-seq results show that



Nrp1 is preferentially expressed in the brain and upregulated in the brains of AD mice.

Nrp1 Is Upregulated in Alzheimer's Disease Brain

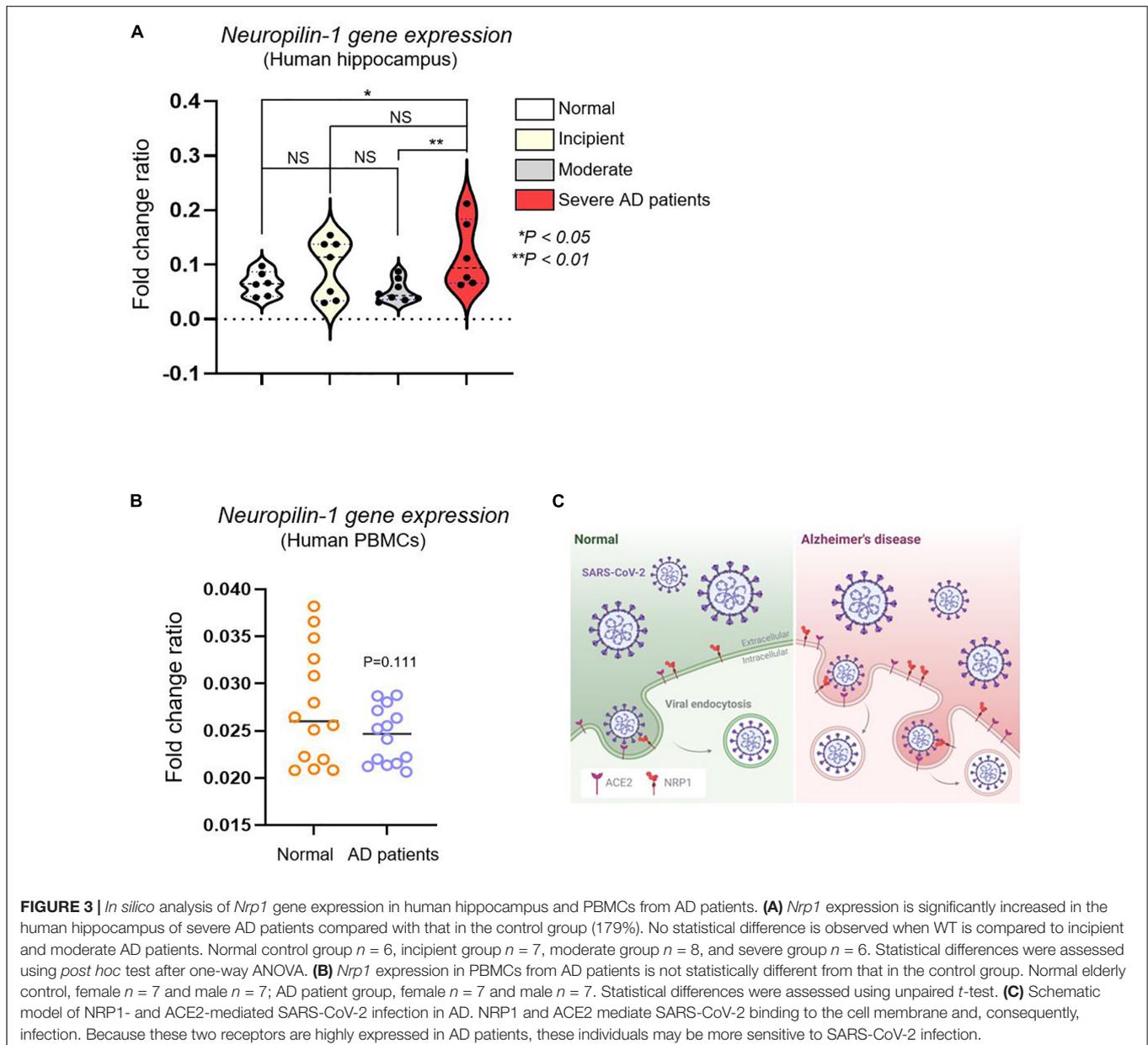
Nrp1 is abundantly expressed in the neurons and plays an important role for axon guidance, regeneration, neuronal plasticity, or various human diseases, such as epilepsy and seizure (Kumanogoh and Kikutani, 2013).

We confirmed *Nrp1* gene expression in both WT and AD model mouse brains through the total RNA-seq (Figure 1). To further analyze *Nrp1* expression during AD progression, we measured the *Nrp1* mRNA levels in 3- to 9-month-old AD brains. RT-qPCR revealed an approximately 145% increase in *Nrp1*

mRNA expression in 9-month-old AD brains compared with that in WT brains (Figure 2A). In addition, NRP1 protein expression was also significantly increased in 9-month-old AD brains compared with that in the WT (Figures 2B,C). Taken together, these findings indicate that *NRP1* gene and protein expression levels are significantly increased in the brains of aged AD mice.

Severe Alzheimer's Disease Patients Are Highly Expressed With *Nrp1*

Having found increased *Nrp1* gene expression in the brains of AD mice, we next performed *Nrp1* gene expression profiling of brains and PBMCs from human patients with different stages of AD (Supplementary Table 1). To identify the fold change of the ratio for *Nrp1* gene from AD patients, we performed *in silico* analysis



using the GSE1297 and GSE4296 microarray data set. Patients with severe AD showed significantly upregulated *Nrp1* gene expression (179%) compared with the control group (individuals without AD), whereas incipient and moderate AD patients did not show increases in brain *Nrp1* gene expression (**Figure 3A**). Interestingly, we did not find differences in PBMC *Nrp1* gene expression between any of the groups (**Figure 3B**). These data correlate with results from the AD murine model. Together, the results demonstrate that NRP1 mRNA and protein expression is significantly elevated in the brains of late-stage AD patients.

DISCUSSION

Since the beginning of the COVID-19 pandemic, there have been significant efforts to identify unique SARS-CoV-2-associated proteins that could serve as targets for novel vaccines or therapeutic agents. Despite notable studies suggesting the possibility of developing other COVID-19-targeted drugs, the first-generation drugs have mostly focused on the viral spike protein receptor ACE2 (Yin et al., 2020). As high-throughput genomic studies begin to define the abnormal expression of individual DNA in particular diseases, it may become possible to rationally determine disease-specific gene expression and, thus, establish biomarkers for risk prediction in older people with complications, such as AD. Recently, we showed the increase of ACE2 expression in an elderly group with AD; therefore, our *in silico* analysis accurately predicts high risk for SARS-CoV-2 infection in elderly patients with AD (Lim et al., 2020). In addition, our research scheme may be useful for predicting the risk of AD in patients with SARS-CoV-2 infection.

Our findings have implications for the prevention and treatment of SARS-CoV-2 infection in elderly patients with AD. First, both *Ace2* and *Nrp1* are preferentially expressed in the brain, and their expression level may determine the sensitivity to SARS-CoV-2 infection (**Figure 3C**). Interestingly, it was recently suggested that differences in cytokines, such as IL-1 β and TNF- α , are less pronounced in peripheral blood in SARS-CoV-2 infection (Totura and Baric, 2012; Tincati et al., 2020). Second, in addition to *Ace2*, *Nrp1* expression was also upregulated in patients with severe AD. Although predictive immune biomarkers are suggested for the clinical treatment of COVID-19 (Fouladseresht et al., 2020), our high-throughput analysis-based approach would probably provide an accurate prediction of SARS-CoV-2 risk in elderly AD patients. Notably, *Ace2* gene expression gradually increased with the severity of AD symptoms (from incipient to severe stage) (Lim et al., 2020), whereas elevated *Nrp1* gene expression was only present in the severe AD patient group (**Figures 1B,C**). This result indicates that ACE2 may be a more fundamental gene for SARS-CoV-2 infection compared with NRP1.

Recently, the spread of SARS-CoV-2 infection has accelerated worldwide. Efforts on the clinical treatment of SARS-CoV-2 infection are concentrated on the development of vaccines and drugs, including gene therapy (Chugh et al., 2020). To our knowledge, this is the first study examining NRP1 expression in

AD patients and reporting its higher expression these individuals. Moreover, it reveals the importance of determining SARS-CoV-2 spike protein receptor gene expression. Our gene profiling could potentially be used to predict the risk for SARS-CoV-2 infection in elderly AD patients.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

ETHICS STATEMENT

All animal experiments performed in this study were reviewed and approved by the IACUC Committee at Korea Brain Research Institute (IACUC-20-00018). Written informed consent was obtained from the owners for the participation of their animals in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

J-YJ and K-HL designed the research. K-HL, SY, S-HK, and J-YJ wrote the manuscript, performed the research, discussed the results, and commented on the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fgene.2021.741175/full#supplementary-material>

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