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Identification of age- and gender-associated long noncoding RNAs in the human brain with Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is an age- and gender-associated brain disorder. Long noncoding RNAs (lncRNAs) have emerged as key regulators of brain development, homeostasis, and pathologies. Here, we used gene array data sets and bioinformatics analysis to identify differentially expressed age- and gender-associated lncRNAs in human AD brains. We found that the expressions of 16 age-associated and 13 gender-associated lncRNAs were dysregulated in AD brains. Notably, the expressions of age-associated lncRNAs—SNHG19 and LINC00672—were significantly correlated with Braak stage of AD, positively and negatively, respectively, whereas the expressions of gender-associated lncRNAs—RNF144A-AS1, LY86-AS1, and LINC00639—were negatively correlated with Braak stage of AD. Functional analysis suggests that the pathways involved in neurodegenerative diseases, synaptic vesicle cycle, and endocytosis were overly represented within age- and gender-associated lncRNA-correlating genes. The identification of age- and gender-associated lncRNAs and their differential expressions in the human AD brain provide potential targets for further experimental validation and mechanistic investigation, which could, in turn, pave the way for developing age- and gender-specific prevention and adjunctive therapeutic options for patients with AD.

1. Introduction

Alzheimer's disease (AD) is a slowly progressive brain disorder characterized by cognitive decline, irreversible memory loss, disorientation, and language impairment (Masters et al., 2015). Aging is one of the major risk factors for AD. In the U.S., more than 10 percent of people aged 65 years and older are living with AD (Masters et al., 2015). Cognitive decline in aging and AD is associated with altered expression of genes involved in synaptic function, energy metabolism (including mitochondrial function), and protein synthesis in the brain (Grimm and Eckert, 2017; Saura et al., 2015). The alteration of age-related genes is accelerated in the brain of patients with AD (Saetre et al., 2011), suggesting aberrant regulation of aging-associated transcripts in the human brain could contribute to AD pathogenesis.

The overall incidence of AD in females is up to twice that of males in the U.S. (Chene et al., 2015; Drew, 2018). Gender differences in brain development, structure, and function are considered as important implications for mechanistic investigation of psychiatric diseases and neurodegenerative disorders including AD (Mazure and Swendsen, 2016). Studies have demonstrated that sex steroids can modulate brain development and are crucial for the development of brain regions, such as the hippocampus and parietal lobe that are significantly affected in AD (Compton et al., 2001; Fitch and Denenberg, 1998; Murphy et al., 1996). For example, plasma levels of circulating sex steroids have been shown positively correlated with cognitive performance in women who undergo bilateral oophorectomy (Sherwin, 1988). Subsequent studies have further demonstrated that the administration of estrogens affects brain organization for memory and improves cognitive ability in postmenopausal women (Shaywitz et al., 1999; Sherwin, 1988). In

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addition, Barnes et al. (Barnes et al., 2005) have demonstrated a stronger correlation between brain pathology (such as neuritic plaques, diffuse plaques, and neurofibrillary tangles) and clinical AD in females than in males, indicating gender differences in the brain could be a significant factor for the development of AD.

Gender-specific gene expression related to brain function has also been implicated in AD pathogenesis. For example, Köglsberger et al. have demonstrated a male-specific reduction of sex-linked ubiquitin-specific peptidase 9 (USP9) in AD (Koglsberger et al., 2017). Mechanistic studies have demonstrated that USP9 is a positive regulator of an AD-associated protein—microtubule-associated protein tau (MAPT). Another elegant study by Bangasser et al. has demonstrated that overexpression of corticotropin-releasing factor (CRF) in females is associated with increased tau phosphorylation—a critical step in the formation of fibrillary tangles that are often observed in AD brains (Bangasser et al., 2017).

Recent compelling evidence has indicated that long noncoding RNAs (lncRNAs) are key mediators in the development and progression of various brain disorders, including AD. A group of differentially expressed lncRNAs, including n341006, and AD-linc1 were identified in human AD brains by Zhou and Xu (2015) and Magistri et al. (2015). Subsequent analysis has revealed a brain-region-specific expression pattern of lncRNAs that is age dependent and AD associated (Zhou et al., 2018).

Herein, we investigated the expression patterns of lncRNAs in the human brain during aging and between genders and their differential expressions in the AD brains. We found that 16 age-associated and 13 gender-associated lncRNAs were dysregulated in AD brains. The functional analysis suggests that these lncRNAs could be pivotal regulators of neuronal functions.

2. Materials and methods

2.1. Microarray data acquisition

Five sets of microarray gene expression data (GSE53890, GSE48350, GSE5281, GSE84422, and GSE66333) were obtained from the Gene Expression Omnibus (GEO) database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/geo/) (Barrett and Edgar, 2006; Barrett et al., 2013). The statistics and description of the data sets are shown in Table 1. Of note, the microarray data set GSE66333 contains expression profiles of neurons isolated from 8 cases (4 high and 4 low oxidative damage and an associated DNA damage response [DDR]) by laser-capture microdissection (Simpson et al., 2016). High and low DDRs are characterized by the robustness of both DNA-protein kinase catalytic subunit (DNA-PKcs) activation and histone H2AX (γH2AX) phosphorylation as reported previously (Shrivastav et al., 2008; Simpson et al., 2015, 2016). The raw data were normalized with the robust multichip average method using the R software "limma" package.

2.2. Reannotation of the affymetrix microarray and identification of differentially expressed lncRNAs

The probe sets of the Affymetrix Human Genome U133 Plus 2.0 array were first reannotated using the method developed by Van Grembergen et al. (2016). Briefly, sequences of all probe sets were locally mapped against a reference transcriptome in the LNCipedia database—a database dedicated to lncRNAs and Ensembl 84 transcriptome. Probes that target lncRNAs in the LNCipedia database remain, whereas probes that are discordant between LNCipedia and Ensembl were discarded from the future analysis. Probe sets that target multiple genes were also excluded unless the targets are duplicated lncRNAs. Long noncoding RNA transcripts were defined as duplicated if more than 95% of one sequence is identical to the other. Finally, 3053 lncRNAs represented by 3668 probe sets were reannotated.

The GEO2R (Barrett et al., 2013) Web tool (http://www.ncbi.nlm.nih.gov/geo/geo2r/) was used to identify differentially expressed genes between 2 given groups of samples in a GEO profile. Long noncoding RNAs with $p \leq 0.05$ and $|\log \text{Fold Change}| \geq 0.5$ were selected for further analysis. The age- and gender-associated lncRNAs were further subjected to coding potential analysis using coding potential calculator (CPC) (Kong et al., 2007) and Coding-Potential Assessment Tool (CPAT) (Wang et al., 2013). Transcripts with the CPC score between −1 and 1 are marked as "weak noncoding" or "weak coding." Transcripts with CPC score < -1 or CPAT score <0.364 were considered as noncoding RNAs.

2.3. Functional enrichment analysis of lncRNAs based on their correlated mRNAs

Pathway enrichment analysis on lncRNA-correlating genes was performed using the R2 KEGG Pathway Finder by Gene correlation (R2: Genomics Analysis and Visualization Platform ; http://r2.amc.nl) using the data set GSE48350 (173 normal and 80 AD brain samples). Genes with a p-value of <0.05 were considered as lncRNA-correlating genes. Pathways with p-value ≤ 0.01 (cutoff 0.01) were considered as having significant over-representation in the data set and were ranked by the sum of the negative log10 p-value of each lncRNA for each pathway.

2.4. Statistical analysis

Using a 2-tailed unpaired t-test or 2-way analysis of variance for differential expression as indicated in the figure legends, p-values were calculated. The linear regression equations were derived based on the average expression of lncRNAs in each age group (20:

Table 1
The statistics and description of the data sets used in this study

Data sets (GEO ID) [a]	Data	Sample type/source	References
GSE53890	41 adult human brains (aged 24–106 y)	Frontal cortical regions	(Lu et al., 2014)
GSE48350	48 normal controls (aged 20–99 y); 21 AD cases (aged 74–95 y)	Superior frontal gyrus	(Astarita et al., 2010; Berchtold et al., 2008; Berchtold et al., 2013; Blair et al., 2013; Cribbs et al., 2012; Sarvari et al., 2012)
GSE5281	23 AD brains (aged 68–95 y); 11 normal controls (aged 63–102 y)	Laser-capture microdissected neurons from the superior frontal gyrus	(Liang et al., 2007; Liang et al., 2008; Readhead et al., 2018)
GSE84422	102 patients (aged 62–102 y; clinical dementia rating: 0–5)	Amygdala and nucleus accumbens	(Wang et al., 2016)
GSE66333	Four high DNA damage responses. Four low DNA damage responses	Frontal cortex pyramidal neurons	(Simpson et al., 2016)

[a] All data sets used in this study were generated on the microarray platform GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array.

[age ranging 20–29, n = 7]; 30: [30–39, n = 5]; 40 [40–49, n = 9]; 60: [52–69, n = 5]; 70: [70–79, n = 8]; 80: [80–89, n = 6]; and 90 [90–99, n = 10]) for the normal brains, where *n* is the age group index. The Pearson correlation coefficients were calculated using the R package and GraphPad Prism, version 6.01, for Windows (GraphPad Software, San Diego, CA, USA).

2.5. Data availability statement

The original data (GSE53890, GSE48350, GSE5281, GSE84422, and GSE66333) used for this study are available at the GEO database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/geo/). Anonymized data will be shared on request from qualified investigators.

3. Results

3.1. Common lncRNA expression patterns identified in aged and AD brains

To explore the expression pattern of lncRNAs in aged and AD brains, we first investigated differentially expressed lncRNAs in the prefrontal cortex of young (≤40 years) and aged (≥80 years) individuals without AD (from the data set GSE53890). As shown in Supplementary Table 1, the expressions of 22 and 22 lncRNAs were upregulated and downregulated, respectively, in the aged brains compared with young adult brains. The dysregulated lncRNAs in aged brains are shown in Fig. 1A. Analysis of the data set GSE48350 demonstrated that the expressions of 18 and 32 lncRNAs were significantly upregulated and downregulated, respectively, in AD brains compared with normal brains (Supplementary Table 2). The dysregulated lncRNAs in AD brains are shown in Fig. 1B. We next compared the significantly regulated lncRNAs in aged brains and AD brains. As shown in Fig. 1C, the expressions of 15 lncRNAs were commonly altered in both aged and AD brains compared with normal brains. Interestingly, all of these lncRNAs were either commonly upregulated (6 lncRNAs) or downregulated (9 lncRNAs) in both aged and AD brains compared with normal brains. As shown in Fig. 1D, the expressions of LINC01094, NEAT1, and LINC00844 were significantly increased in both aged and AD brains with a log2 fold change greater than 1, and the expressions of LINC01007, LINC00507, and OIP5-AS1 were significantly decreased in both aged and AD brains with a log2 fold change less than −1.

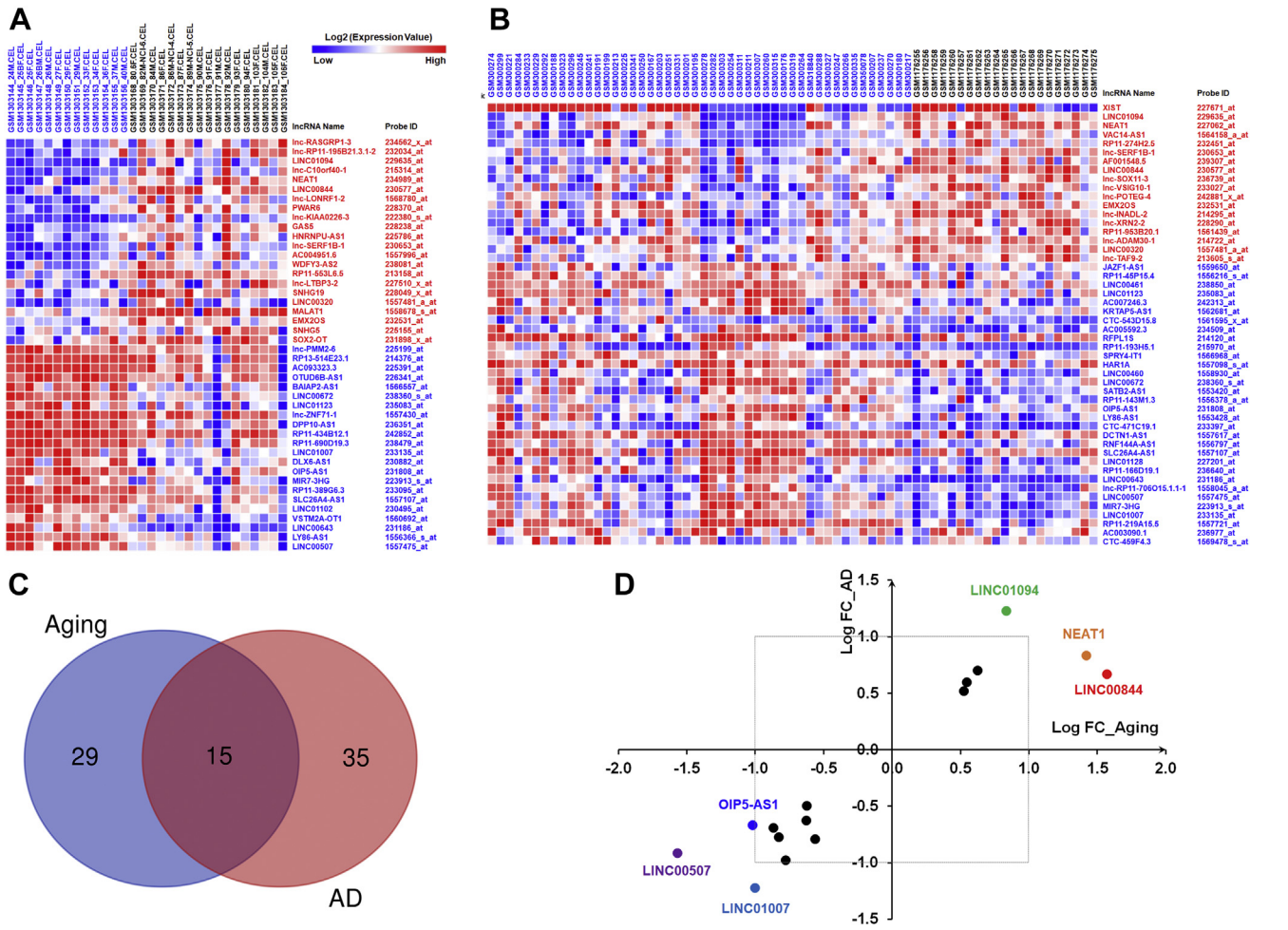

Fig. 1. Common lncRNA expression patterns in the frontal cortices of aged and AD individuals. (A) Heat map showing microarray data (GSE53890) for the upregulated and downregulated lncRNAs in the frontal cortices of aged individuals (age ≥80; n = 17) compared with that in young individuals (age ≤ 40; n = 13). (B) Heat map showing microarray data (GSE48350) for the upregulated and downregulated lncRNAs in the frontal cortices of individuals with AD (n = 21) compared with that in individuals with no disease (nd; n = 48). (C) Venn diagram illustrating the overlap of 15 lncRNAs that were altered [|log2 (Fold Change)| > 0.5; $p < 0.05$] by both aging and AD. (D) Scatter plot illustrating the 15 overlapping lncRNA genes showing log2 of fold change by AD (x-axis) against log2 of fold change with aging (y-axis). The upper right quadrant represents 6 lncRNAs that were increased with both aging and AD. Conversely, the lower left quadrant illustrates 9 lncRNAs that were decreased by both aging and AD. Abbreviations: AD, Alzheimer's disease; lncRNA, long noncoding RNA.

3.2. Abnormal alteration of age-associated lncRNAs in AD brains

Next, we sought to determine whether there is an abnormal alteration in the expression level of age-correlated lncRNAs in AD brains. For this, we retrieved microarray expression profiles of the human frontal cortex (GSE53890) and performed Pearson's correlation analysis between age and log2 expression value. As shown in Fig. 2A and Supplementary Table 3, the expressions of 23 lncRNAs were negatively correlated with age and the expressions of 29 lncRNAs were positively correlated with age (all $|r| > 0.5$; $p < 0.05$). To further confirm that the expressions of these lncRNAs were correlated with age and to investigate their alterations in AD brains, we first, using data retrieved from GSE48350, performed Pearson's correlation analysis between the average log2 expression value of each lncRNA in each age group (normal brain with no AD) and age index; next, we conducted a 95% prediction interval for the regression slope for each lncRNA followed by expression comparison between AD and normal brains within each age group. As shown in Fig. 2B–Q, the expressions of 16 lncRNAs were strongly correlated with age in individuals with no diseases (all $|r| > 0.75$; $p < 0.05$), either positively or negatively, while their expressions in AD brains fell outside of their prediction intervals calculated based on their expression in normal aging brains, indicating the expressions of these 16 lncRNAs were abnormally alternated in AD brains during aging. For example, the expressions of the positively correlated age-associated lncRNAs—LINC00844, PRR34-AS1, and

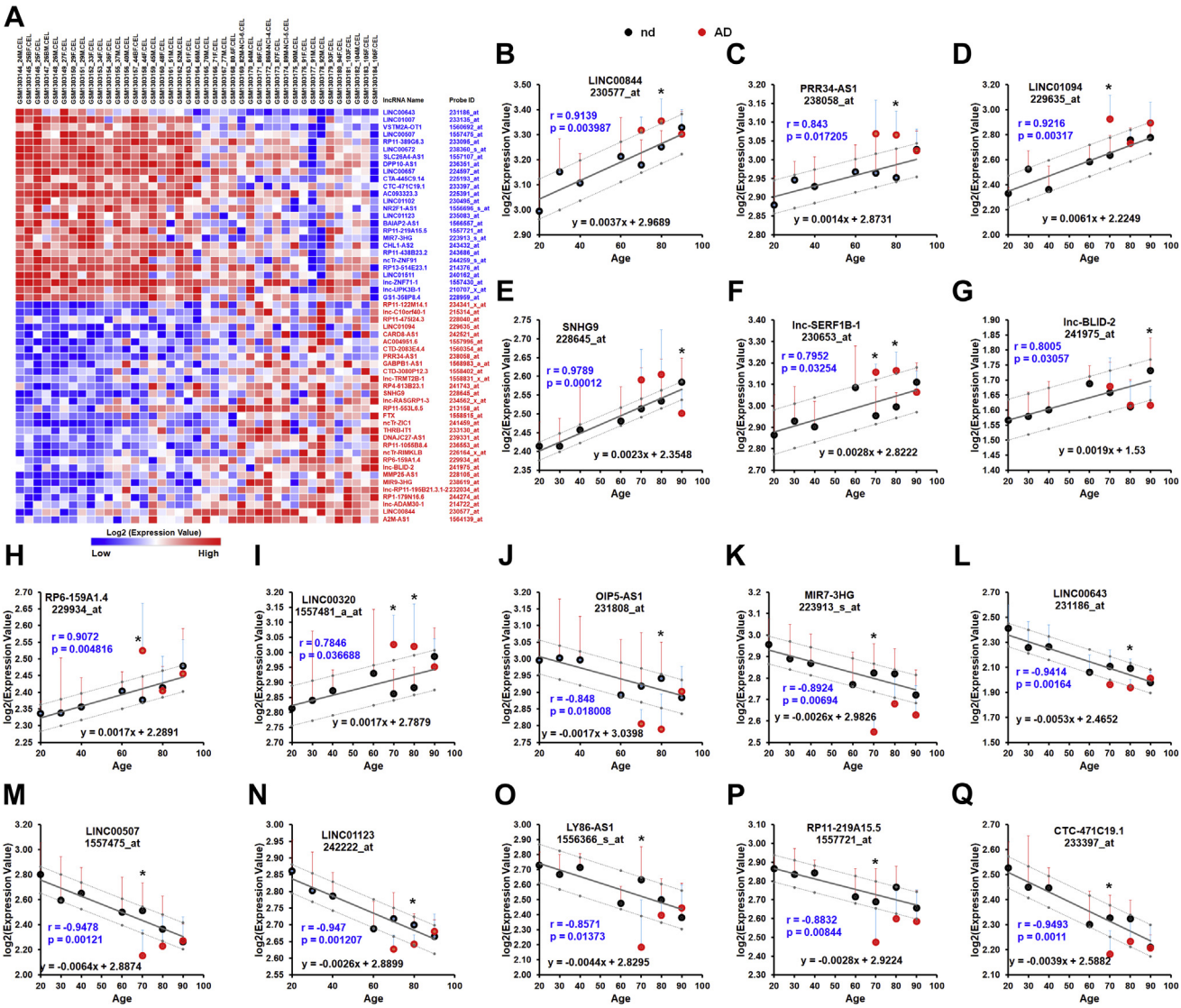

Fig. 2. Abnormal alteration of age-associated lncRNAs in the frontal cortices of patients with AD. (A) Heat map representation of microarray data (GSE53890) for age-correlated lncRNAs ($|r| > 0.5$; $p < 0.05$; Pearson's test). Blue and red colors indicate lncRNAs that are negatively and positively associated with age, respectively. (B–Q) Relative alterations of indicated lncRNAs in the frontal cortices of individuals with no disease (nd; black dots) and AD (red dots) during aging. Bars indicate SD; r and p values were obtained by Pearson's correlation and are shown within the graphs. The black dots with error bars denote means for expression levels of indicated lncRNAs in the frontal cortices of individuals with nd in each age group (20: [age ranging 20–29, n = 7]; 30: [30–39, n = 5]; 40 [40–49, n = 9]; 60: [52–69, n = 5]; 70: [70–79, n = 8]; 80: [80–89, n = 6]; and 90 [90–99, n = 10]). The red dots with error bars denote means for expression levels of indicated lncRNAs in the frontal cortices of individuals with AD in each age group (70: [70–79, n = 3]; 80: [80–89, n = 8]; and 90: [90–99, n = 8]). The solid line shows the expression trend of indicated lncRNA in the frontal cortices during normal aging. Pearson correlation coefficients (r) and p values are shown in the graphs. The dotted lines show the 95% prediction interval of linear regression analysis calculated from the data set (GSE48350). p-values were calculated using 2-tailed unpaired t-test, where $^{*}p < 0.05$ versus the same age group. Abbreviations: AD, Alzheimer's disease; lncRNA, long noncoding RNA. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

LINC01094—were abnormally increased in AD brains compared with age-matched normal brains (Fig. 2B–D). In contrast, the expressions of the negatively age-associated lncRNAs—MIR7-3HG, LINC00643, and LINC00507—were significantly decreased in AD brains compared with age-matched normal brains (Fig. 2K–M).

3.3. Dysregulated gender-associated lncRNAs in AD brains

To determine gender-associated lncRNAs and their alterations in AD brains, we first compared differentially expressed lncRNAs in 4 comparison pairs: (1) female (n = 24) versus male (n = 24) in individuals with no diseases; (2) female (n =12) versus male (n = 7) in patients with AD; (3) female with AD versus female with no diseases; and (4) male with AD versus male with no diseases (Data from the data set GSE48350). As shown in Fig. 3A, a total of 37 (13 + 10 + 11 + 3) lncRNAs were differentially expressed [|log2 (Fold Change)| > 0.5; $p < 0.05$] in female versus male normal brains. Among them, 3 and 11 lncRNAs were also differentially expressed in female AD brains and male AD brains compared with female and male normal brains, respectively (red circles in

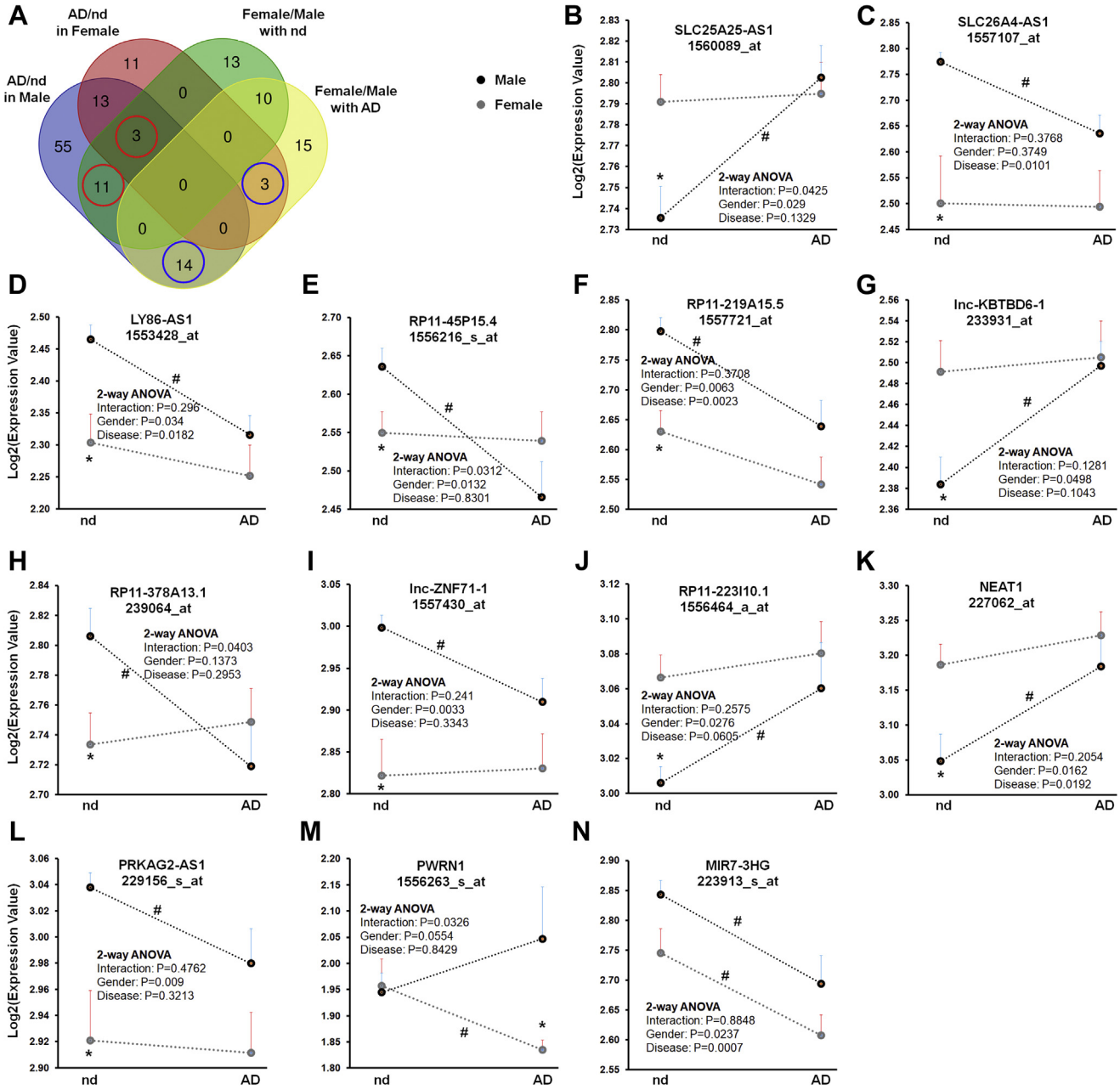

Fig. 3. Dysregulated gender-associated lncRNAs in the frontal cortices of AD patients. (A) Venn graph summarizes the number of common and unique lncRNAs (data set GSE48350) identified in the 4 comparisons: Female (n = 24) versus male (n = 24) in individuals with no disease (nd), female (n = 12) versus male (n = 7) in patients with AD, female with AD versus female with nd and male with AD versus male with no disease (nd). Red circles indicate numbers of gender-associated (female vs male normal brains) lncRNAs differentially expressed in female AD brains vs female normal brains and male AD brains vs male normal brains. Blue circles indicate numbers of gender-associated (female vs male AD brains) lncRNAs differentially expressed in female AD brains vs female normal brains and male AD brains vs male normal brains. (B–N) Relative expression of indicated lncRNAs in the frontal cortices of male (black dots) and female (gray dots) individuals with and without AD (GSE48350). To avoid age bias, a total of 43 subjects, age ranging from 70 to 99, (9 males and 13 females with nd; 7 males and 14 females with AD), were selected for this analysis. Bars indicate SEM. *p*-values were calculated using 2-tailed unpaired *t*-test where: $^{*}p < 0.05$ versus male in the same disease status; # $p < 0.05$ versus no disease in the same gender. Results of 2-way ANOVA are given within the graphs. Abbreviations: AD, Alzheimer's disease; lncRNA, long noncoding RNA.

Fig. 3A). A total of 42 lncRNAs were differentially expressed in female and male AD brains. Among them, 3 and 14 of them were differentially expressed in female and male AD brains compared with female and male normal brains, respectively (blue circles in Fig. 3A). Next, to avoid age bias, data from a total of 43 individuals, age ranging from 70 to 99, (9 males and 13 females with no disease; 7 males and 14 females with AD), were selected for further analysis. As shown in Fig. 3B–N and Supplementary Table 4, the expressions of 13 gender-associated lncRNAs were significantly dysregulated in AD brains compared with normal brains in either females or males. For example, SLC25A25-AS1 shows lower levels in normal male brains compared with normal female brains but was significantly upregulated in male AD brains specifically compared with normal male brains (Fig. 3B). PWRN1 was expressed at similar levels in normal female and male brains, whereas the expression of PWRN1 was significantly decreased in female AD brains specifically (Fig. 3M). Interestingly, 2-way analysis of variance (gender × AD) demonstrated a significant interaction and significant main effects of gender on the expressions of SLC25A25-AS1 and RP11-45P15.4 (Fig. 3B and E), indicating that AD affects the expression of the gender-associated lncRNAs in a gender-dependent manner.

Next, we sought to determine the coding potential of the age- and gender-associated lncRNAs. For this, CPC and CPAT were applied to evaluate the coding potential of the age- and gender-associated lncRNAs. As shown in Supplementary Table 5, all of the 16 age-associated and 13 gender-associated lncRNAs that were dysregulated in AD brains are noncoding or have weak potential coding RNAs.

3.4. Correlation of the age- and gender-associated lncRNAs with Braak stage of AD and their host genes

We next sought to determine whether the expressions of these lncRNAs are correlated with disease stage using age-matched samples in the data set GSE48350 (Supplementary Table 6). To this end, we performed Pearson's correlation analysis between the average log2 expression value of each lncRNA in each Braak stage and Braak stage of AD (normal was considered as 0). As shown in Fig. 4A, the expression of the age-associated lncRNA LINC00672 was negatively correlated with Braak stage of AD. As shown in Fig. 4B–E, the expression of the age-associated lncRNA SNHG19 was positively correlated with Braak stage of AD, whereas the expressions of gender-associated lncRNAs (RNF144A-AS1, LY86-AS1, and LINC00639) were negatively correlated with Braak stage of AD.

We next asked whether expressions of the age- and gender-associated lncRNAs are correlated with neuritic plaque density, which is one of the major histopathological lesions of AD. To this end, we computed correlations between the log2 expression value of the age- and gender-associated lncRNAs and average neuritic plaque density using data in the data set GSE84422, which was generated on the GPL507 microarray platform. Interestingly, as shown in Supplementary Fig. 4, the expressions of 4 lncRNAs, such as RP11-223I10.1, LINC01094, OIP5-AS1, and LINC01007, showed a moderate linear correlation with average neuritic plaque density ($|r| > 0.3$ and $p < 0.05$, $n = 102$).

In addition, given the fact that expression of lncRNA often correlates with the expression of its host or neighbor genes because of

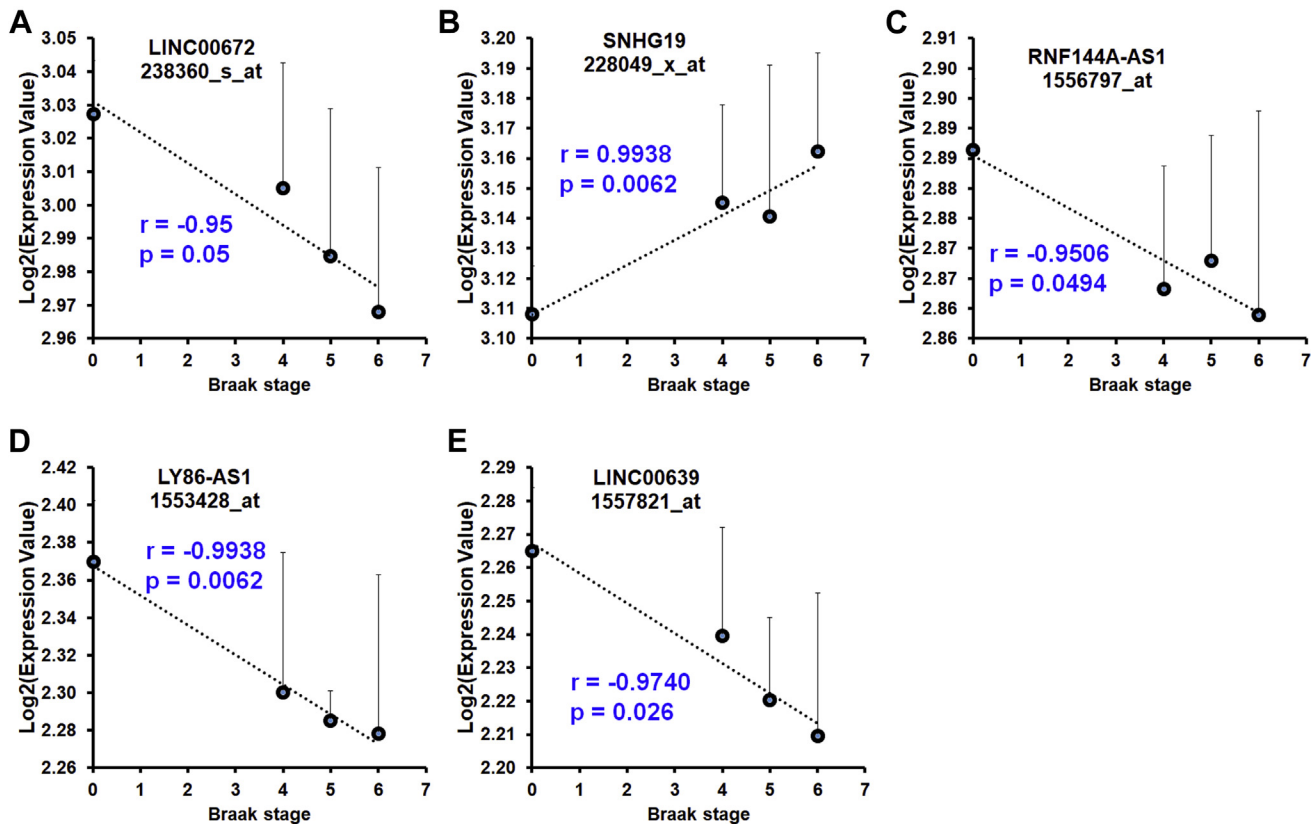

Fig. 4. Expression of aging- and gender-associated lncRNAs was correlated with Braak stage of AD in the anterior PFC. (A–E) Expression of age-associated lncRNAs—LINC00672 (A) and SNHG19 (B)—was positively and negatively correlated with Braak stage of AD, respectively, whereas the expression of gender-associated lncRNAs—RNF144A-AS1 (C), LY86-AS1 (D), and LINC00639 (E)—was negatively correlated with Braak stage of AD. Pearson's correlation coefficient r and p-values are indicated in the figure. (Data set GSE48350; n = 22 for no disease, age ranging from 70– to 99 years; n = 6 for Braak stage of IV; n = 4 for Braak stage of V; n = 5 for Braak stage of VI). Abbreviations: AD, Alzheimer's disease; lncRNA, long noncoding RNA; PFC, prefrontal cortex.

shared regulatory elements and cis-regulatory role of lncRNA, we, therefore, calculated the Pearson correlation coefficient between each lncRNA-host mRNA pair using the expression values in the data set GSE48350 (173 normal and 80 AD brain samples). We found that the expressions of 9 lncRNAs have positive correlations with the expressions of their intersecting mRNAs, whereas the expressions of 2 lncRNAs have positive correlations with the expressions of their intersecting genes ($|r| > 0.5$, $p < 0.0001$; Supplementary Fig. 5).

3.5. Dysregulation of age- and gender-associated lncRNAs in neurons of patients with AD

To determine whether the alteration of the age- and gender-associated lncRNAs is neuron specific, we assessed the data set GSE5281 that contains gene expression profile in neurons from the superior frontal gyrus of AD cases and normal controls (Liang et al., 2008). Interestingly, most of the age- and gender-associated lncRNAs showed similar alteration in the neurons from AD brains compared with normal brains (Fig. 5 and Supplementary Figures 1 and 2). For example, negatively correlated age-associated lncRNAs—LY86-AS1, RP11-219A15.5, MIR7-3HG, LINC01007, and LINC00643—were significantly downregulated in the neurons of patients with AD compared with controls (Fig. 5A–E), whereas age positively correlated lncRNAs—NEAT1, PRR34-AS1, and lnc-BLID-2—were significantly upregulated in the neurons of patients with AD compared with controls (Fig. 5F–H). However, as shown in Fig. 5I, the expression of OIP5-AS1 (age negatively correlated) was significantly upregulated in the neurons of patients with AD compared with controls, indicating a distinct alteration pattern of OIP5-AS1 in various central nervous system cells, such as increased in the AD neurons but likely decreased in the AD glial cells.

Oxidative damage and an associated DDR occur at the earliest stages of Alzheimer pathology (Simpson et al., 2010, 2016) and could be reflected by AD-associated lncRNAs. We thus sought to assess the expression of the AD-associated lncRNAs in neurons isolated from brains with a high and low neuronal DDR from the data set GSE66333 (Simpson et al., 2016). Interestingly, as shown in Supplementary Fig. 3 and Supplementary Table 4, the down-regulated lncRNAs in AD brains were expressed at higher levels in neurons isolated from high-DDR cases than from low-DDR cases, which further suggests that high levels of oxidative stress and an associated neuronal DDR are very early events in the progression of AD and the downregulation of the AD-associated lncRNAs in AD neurons could be triggered by these events.

3.6. Functional analysis of age- and gender-associated lncRNAs

Finally, to investigate the potential functions of the age- and gender-associated lncRNAs in AD brains, pathway enrichment analysis on lncRNA-correlating genes was performed using the R2 KEGG Pathway Finder. Data used for the correlation analyses were from the GSE48350 data set (173 normal and 80 AD brain samples) in the R2 platform. Supplementary Table 7 shows the KEGG pathways that were significantly over-represented within the age- and gender-associated lncRNA-correlating genes. The pathways were then ranked by the sum of the negative log10

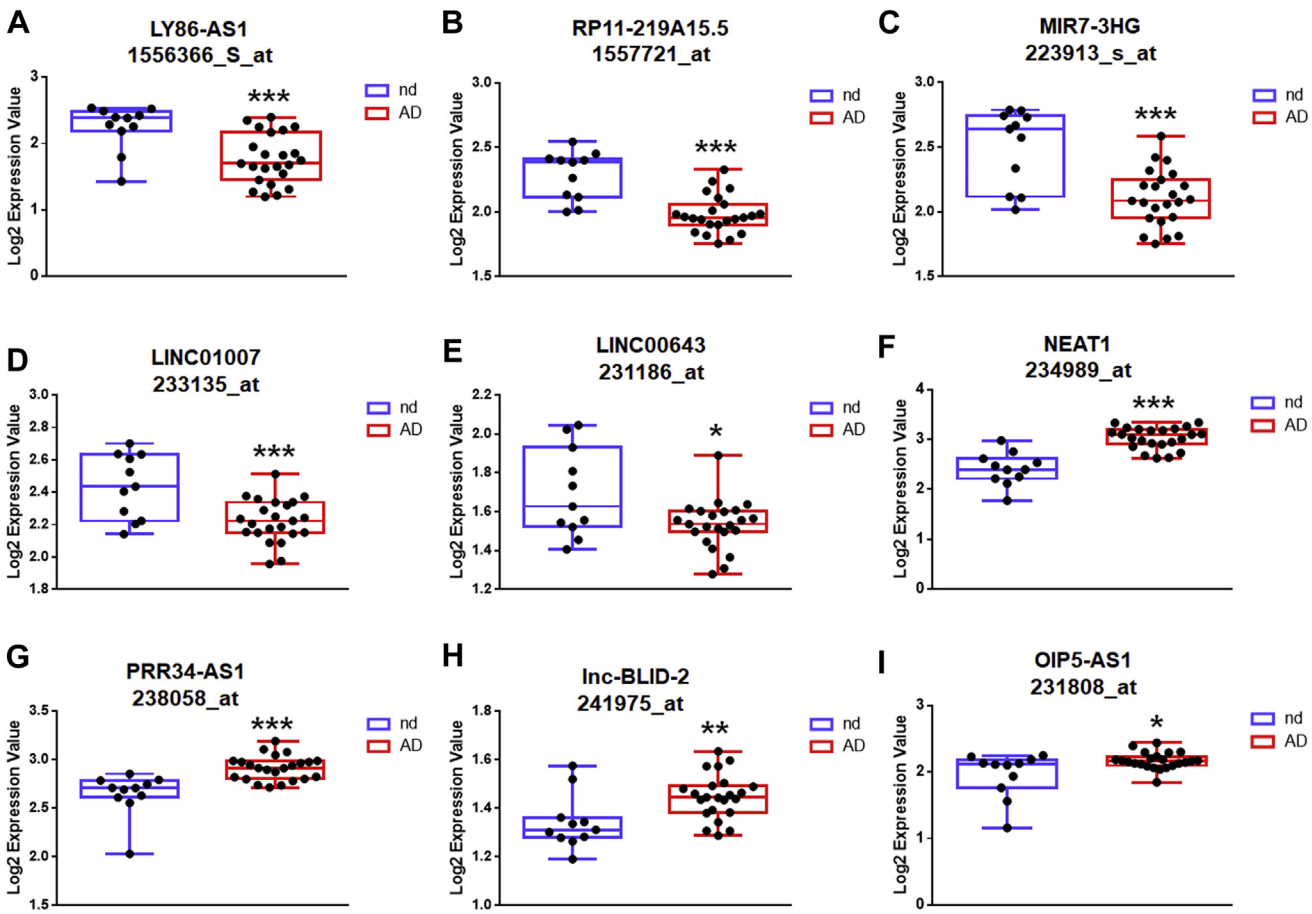

Fig. 5. Age-associated lncRNAs are dysregulated in neurons of patients with AD. (A-I) Boxplots of expression levels of age-associated lncRNAs in frontal neurons of individuals with no disease (nd, n = 11) and AD (n = 23) based on the GSE5281 data set. Boxplots show median, interquartile range, sample minimum, and maximum. *p*-Values were calculated using 2-tailed unpaired *t*-test, where $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. Abbreviations: AD, Alzheimer's disease; lncRNA, long noncoding RNA.

p-value of each lncRNA for each pathway. Top 30 pathways are shown in Fig. 6. Interestingly, KEGG pathways involved in neurodegenerative diseases, such as AD, HD, and PD (Huntington's, and Parkinson's disease), were over-represented within both age- and gender-associated lncRNA-correlating genes. Endocytosis and Prostate_cancer KEGG pathways were significantly correlated with AD-, age-, and gender-associated lncRNAs (Fig. 6A and B). Notably, lysosome and TNF_signaling pathways were in the top 30 enriched pathways among age- and AD-associated lncRNA-correlating genes (Fig. 6A), whereas Glioma and FoxO_signaling pathways were in the top 30 significantly over-represented pathways of gender- and AD-associated lncRNA-correlating genes (Fig. 6B). Furthermore, proteasome and Long_term_potentiation KEGG pathways were commonly correlated with both age- and gender-associated lncRNAs in normal brains (Fig. 6C and D).

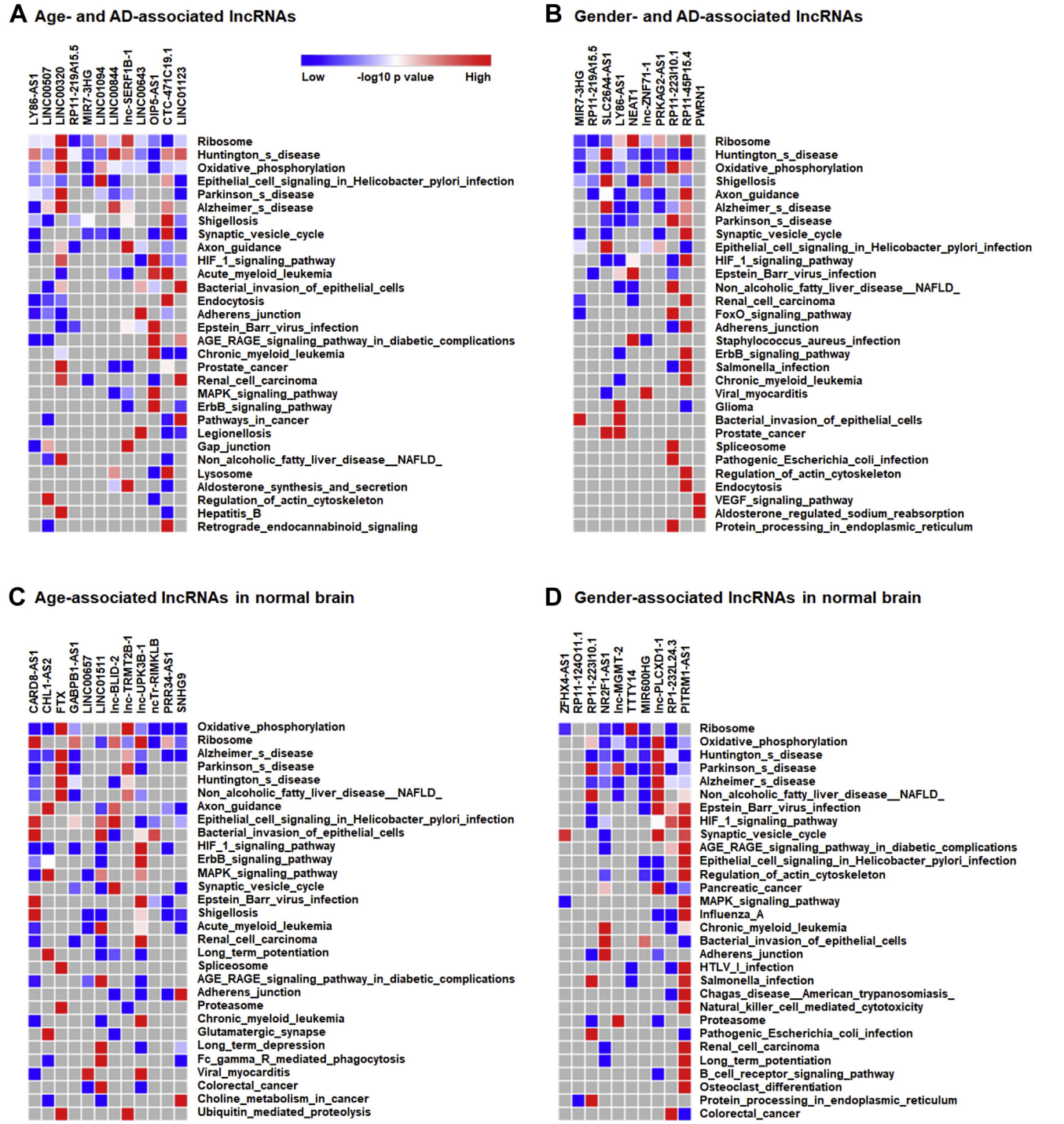

Fig. 6. Top 30 KEGG pathways significantly correlated with the expression of lncRNAs associated with age (A) and gender (B) in human AD brains and age (C) and gender (D) in normal brains. Each column corresponds to a single lncRNA, and each row corresponds to a KEGG pathway with an overrepresentation of genes correlating with lncRNA. The pathways were ranked by the sum of the negative log10 *p*-value of each lncRNA for each pathway. Top 30 pathways are shown. Abbreviations: AD, Alzheimer's disease; lncRNA, long noncoding RNA.

4. Discussion

In the present study, we investigated the expression patterns of lncRNAs in the human brain during aging and between genders as well as their differential alterations in human AD brains. We found that the expressions of 18 age-associated and 13 gender-associated lncRNAs were dysregulated in AD brains compared with normal brains. Moreover, the expressions of age-associated lncRNAs—SNHG19 and LINC00672—were positively and negatively correlated with Braak stage of AD, respectively, whereas the expressions of gender-associated lncRNAs—RNF144A-AS1, LY86-AS1, and LINC00639—were negatively correlated with Braak stage of AD. Further functional analysis suggests that these lncRNAs could function as key players in a broad array of essential signaling pathways, including ribosome, endocytosis, synaptic vesicle cycle, and axon guidance, that are critical for AD pathogenesis.

Independent lines of evidence suggest that lncRNAs are a new class of players involved in the development and progression of brain aging, cognitive decline, and AD. For example, the study by Faghihi et al. (2008) have demonstrated that the BACE1-antisense transcript (BACE1-AS) is concordantly expressed with BACE1 (β-site amyloid precursor protein cleaving enzyme 1, also known as β-secretase—an enzyme central to the pathology of AD; Querfurth and LaFerla, 2010) and acts as a feed-forward positive regulator of BACE1. Moreover, Mus et al. (2007) have demonstrated a steady decrease of a brain-specific lncRNA (BC200) with aging. However, the level of BC200 is significantly upregulated in AD brains compared with age-matched normal brains (Mus et al., 2007). Indeed, studies have shown that BC200 is involved in regulating neuronal protein translation that subsequently could contribute to amyloid plaque formation and AD pathogenesis (Muddashetty et al., 2002; Roberts et al., 2014; Tiedge et al., 1993). In addition, comprehensive studies have identified a group of lncRNAs with aberrant expression in human AD brains (Magistri et al., 2015; Zhou and Xu, 2015) and aged brains (Kim et al., 2016; Kour and Rath, 2016). By analyzing 2 microarray data sets, we here identified a total of 23 lncRNAs that were negatively correlated with age and 29 lncRNAs that were positively correlated with age ($|r| > 0.5$; $p < 0.05$). Furthermore, the expressions of 18 age-correlated lncRNAs, including LINC00844, LINC01094, LINC00507, and OIP5-AS1, were abnormally alternated in AD brains compared with age-matched normal brains. The functioning of the age-associated lncRNAs, however, remains largely unknown. Our functional analysis suggests that the pathways involved in protein synthesis and neuronal functioning such as ribosome, synaptic vesicle cycle, and lysosome were over-represented within the age-associated lncRNA-correlating genes. It is well documented that lysosomal dysfunction in the brain results in a failure to clear accumulated protein aggregates which in turn contributes to the process of aging and pathogenesis of various neurodegenerative diseases (Fraldi et al., 2016; Kaur et al., 2017; Leeman et al., 2018). In the present study, we found the alterations of 3 age-associated lncRNAs (LINC00844, LINC00643, and OIP5-AS1) were abnormally alternated in AD brains, and lysosome was one of the significantly over-represented pathways of the lncRNA-correlating genes, indicating these lncRNAs could serve as master regulators. The underlying mechanisms(s) by which these lncRNAs regulate lysosomal function in aging and AD, however, warrants further investigation.

Females are at higher risk of developing AD than males. Studies have demonstrated that gender differences in genetic risk factors, including apolipoprotein E, known as APOE, is associated with an increased risk for AD. Females with APOE4 are more at risk to develop AD than males with APOE4 (Altmann et al., 2014; Farrer et al., 1997). Recent studies have also demonstrated that single nucleotide polymorphisms, including sex-specific single nucleotide polymorphisms, are associated with AD pathology (Gusareva et al., 2018; Wachinger et al., 2018). Whether gender-associated lncRNAs are differentially expressed in AD brains and their functions in AD pathogenesis, however, are uncertain. Herein, we identified 13 gender- and AD-associated lncRNAs, including SLC25A25-AS1, PWRN1, and LY86-AS1 that were significantly dysregulated in AD brains compared with age-matched normal brains in either females or males. Functional analysis suggests that FoxO_signaling and Glioma pathways were over-represented within the gender-associated lncRNA-correlating genes. Further investigations, however, are needed to better understand the role of these gender-associated lncRNAs in AD pathology.

The frontal cortex, located at the very front of the brain, controls cognitive functions in humans (Fuster, 2002). The superior frontal gyrus is the upper part of the frontal cortex and primarily involved in higher cognitive functions and working memory (du Boisgueheneuc et al., 2006). Structural and gene expression changes in the superior frontal gyrus have been demonstrated in both normal aging and AD (Bakkour et al., 2013). In the present study, we first identified age-associated lncRNAs, such as LINC00844, in the frontal cortex during normal aging. We then confirmed that the expressions of some of the age-associated lncRNAs were also age-correlated in the superior frontal gyrus during normal aging but is abnormally alternated in the superior frontal gyrus of patients with AD, such as LINC00507.

Interestingly, a recent study has demonstrated that NEAT1 is significantly upregulated in the temporal cortex and hippocampus of patients with AD (Spreafico et al., 2018). The authors have further demonstrated that NEAT1 plays a neuroprotective role through regulating cyclin-dependent kinase 5 regulatory subunit 1 (CDK5R1), an AD-associated gene. In addition, LINC00507 has been recently implicated as an age-dependent lncRNA that is expressed in a cortex-specific manner in both nonhuman primates and humans (Mills et al., 2016). In another study, Kang et al. have demonstrated an increase in BACE1-AS levels in the superior temporal gyrus of patients with AD (Kang et al., 2014). Increased BACE1-AS can stabilize BACE1 mRNA and promote BACE1 expression (Faghihi et al., 2008), which, in turn, promote the cleavage of amyloid precursor protein and the accumulation of toxic aggregates of Aβ peptide and ultimately contribute to AD pathogenesis (Kang et al., 2014). Strikingly, Zhou et al. (2018) have recently performed a comparative study on the expression pattern of lncRNAs in 4 brain regions of aged or AD patients and demonstrated that the alteration of age- and AD-associated lncRNAs in the brain is region dependent. The function of these age-associated, AD-associated, and brain-region-associated lncRNAs, however, warrants further, in-depth, investigations.

Although the major findings of this study were reproducible in 2 independent data sets, there are several limitations. First, for the analysis of the correlation between the expression of lncRNAs and Braak stage of AD, there were only 4 and 5 samples for stage V and VI, respectively. Larger sample size will lead to more reliable results. To this end, data sets generated from different platforms and/or studies may be integrated, which will allow us to perform a large-scale meta-analysis. Second, experimental validation will provide more insight into the differential alterations of the age- and gender-associated lncRNAs in AD brains and their actual functions. Third, other clinical factors, such as treatments, body mass index, smoking status, and sample heterogeneity, which could dysregulate the expression of lncRNAs, were not considered in this study.

Taken together, the identification of age- and gender-associated lncRNAs and their differential alterations in the human AD brain provide potential targets for further mechanistic investigation, which could, in turn, pave the way for developing age- and gender-specific diagnosis, prevention, and individualized treatment options for patients with AD.

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Appendix A. Supplementary data

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