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Original Article

Genetic overlap between cortical brain morphometry and frontotemporal dementia risk

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Frontotemporal dementia (FTD) has a complex genetic etiology, where the precise mechanisms underlying the selective vulnerability of brain regions remain unknown. We leveraged summary-based data from genome-wide association studies (GWAS) and performed LD score regression to estimate pairwise genetic correlations between FTD risk and cortical brain imaging. Then, we isolated specific genomic loci with a shared etiology between FTD and brain structure. We also performed functional annotation, summary-data-based Mendelian randomization for eQTL using human peripheral blood and brain tissue data, and evaluated the gene expression in mice targeted brain regions to better understand the dynamics of the FTD candidate genes.
Pairwise genetic correlation estimates between FTD and brain morphology measures were high but not statistically significant. We identified 5 brain regions with a strong genetic correlation ($r_g > 0.45$) with FTD risk. Functional annotation identified 8 protein-coding genes. Building upon these findings, we show in a mouse model of FTD that cortical N-ethylmaleimide sensitive factor (*NSF*) expression decreases with age. Our results highlight the molecular and genetic overlap between brain morphology and higher risk for FTD, specifically for the right inferior parietal surface area and right medial orbitofrontal cortical thickness. In addition, our findings implicate *NSF* gene expression in the etiology of FTD.

Key words: frontotemporal dementia; gene expression; genetic overlap; MRI; neuroimaging.

Introduction

Frontotemporal dementia (FTD) is a heterogeneous spectrum comprising a cluster of neurodegenerative clinical syndromes (Goedert et al. 2012). It is classified based on its 3 clinical subconditions, including the behavioral, language, and motor variants (Leroy et al. 2021). FTD is commonly underdiagnosed, and its point prevalence has been estimated between 15 and 22 per 100,000 people, representing between 10% and 20% of all dementia cases (Onyike and Diehl-Schmid 2013). Although its clinical manifestations, such as psychiatric prodrome, neuropsychiatric symptoms, and language difficulties, are well known, these come in various presentations and severity, ultimately representing a challenge for diagnosis (Bott et al. 2014).

MRI is a noninvasive imaging technology that delineates structural and functional alterations of the brain, which has been proposed as a tool for diagnosing FTD (Cajanus et al. 2018; Bruun et al. 2019; Yu et al. 2021). Several observational and clinical studies using brain imaging techniques have reported associations between brain morphology and FTD (Bruun et al. 2019; Yu et al. 2021). For instance, lesions on the parietal and frontal cortex, which are commonly affected by FTD, have been linked with cognitive decline (Bisbing et al. 2015). Furthermore, it has been demonstrated that atrophy in the orbitofrontal cortex, the medial and lateral prefrontal cortex, the anterior cingulate, and the insula cortex is associated with behavioral symptoms observed in FTD, such as apathy, disinhibition, loss of empathy, and aggression (Whitwell 2019).

Neuroimaging genetics studies, which integrate brain imaging and individual-level genetic data to elucidate the genetic factors influencing brain structure (Mufford et al. 2017), have shed light on the pathophysiological characteristics of these FTD subtypes (Convery et al. 2019; Häkkinen et al. 2020). For instance, findings from neuroimaging genetics studies suggest that abnormalities in functional connectivity networks, gray matter volume, and white matter integrity are detectable before FTD onset and influenced by genetic variation (Häkkinen et al. 2020). Nonetheless, the genetic and neurobiological mechanisms underlying FTD and its subtypes remain largely unknown.

In the present study, we sought to identify brain regions with shared genetic and molecular basis. To that end, we leveraged summary data of genome-wide association studies (GWAS) of individuals of European ancestry to investigate the genetic overlap between 216 brain imaging phenotypes and FTD. We conducted pairwise GWAS (GWAS-PW) analyses to identify specific

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shared genomic regions for FTD and brain regions of interest and performed functional annotation analysis to provide meaningful insights into the underlying biological processes involved in the disease etiology.

Materials and methods

FTD GWAS data

We leveraged publicly available GWAS summary statistics for FTD, including 2,154 cases and 4,308 controls of European ancestry. Briefly, patients were genotyped using Illumina Human 370 K, 550 K, and 660 K Quad Beadchips and Omni Express chips (Illumina Inc, CA, United States). The GWAS was performed under strict quality control methods (Ferrari et al. 2014). A detailed description of these GWAS summary statistics is available in their corresponding publication (Ferrari et al. 2014).

Neuroimaging GWAS data

We leveraged publicly available GWAS summary statistics from the Oxford Brain Imaging Genetic Server—BIG40 (Smith et al. 2021). This database contains hemispheric independent MRI brain measurements of 33,224 individuals of European ancestry based on UK Biobank data. Notably, the BIG40 dataset presents genetic association analyses performed independently for brain regions of interest located in each hemisphere of the brain, which is relevant for FTD-related analyses, given that damage to the right or left temporal lobes results in different clinical manifestations (Irwin et al. 2018). Furthermore, the UK Biobank is a prospective epidemiological study of approximately half a million individuals between 40 and 69 years old (Bycroft et al. 2018). In the present study, we included MRI brain measurements, as processed by WIN FMRIB using FMRIB's Automated Segmentation Tool (Zhang et al. 2001; Alfaro-Almagro et al. 2018; Smith et al. 2021), corresponding to the FreeSurfer segmentation pipeline that includes volume, thickness, and surface area parcellation data based on the Desikan-Killiany aparc parcellation ($n = 216$).

Linkage Disequilibrium Score Regression genetic correlation

We used Linkage Disequilibrium Score Regression (LDSC) (Bulik-Sullivan et al. 2015) to measure the genetic overlap between FTD and FreeSurfer DK morphological measurements. The LDSC method accounts for possible confounding due to sample overlap. In addition, we used a "Bonferroni" correction to account for multiple testing with a corrected *P*-value for a statistically significant significance of 0.0002 (0.05/216 FreeSurfer DK segmentation measurements). We also used a *K*-means algorithm integrated into the R package "pheatmap," rstudio v.4.0.2, to cluster the regions according to their correlation with FTD.

GWAS-PW analyses

We used the GWAS-PW method on highly correlated regions with FTD ($r_g > 0.45$) to identify specific genomic regions shared between FTD and brain morphology measurements. Briefly, GWAS-PW evaluates the genetic overlap over specific genomic regions by splitting the genome into 1,703 segments and estimating the posterior probability of association (PPA). To account for potential confounding due to sample overlap between GWASs of brain MRIs and FTD, we used the correlation between effect sizes of single-nucleotide polymorphisms (SNPs) with a PPA < 0.2, which was calculated in fGWAS (Huang et al. 2017) as a proxy for sample overlap.

For each brain imaging phenotype and genomic region, GWAS-PW estimates the posterior probability of 4 parallel models: (i) the region is unique to FTD, (ii) the region is unique to the imaging phenotype, (iii) both phenotypes share the region through the same genetic variants, and (iv) the region is associated with both phenotypes but through different genetic variants.

Functional annotation and eQTL

SNPs identified in shared regions in GWAS-PW (model 3 with PPA > 0.05) were subjected to functional annotation as implemented in the FUMA platform (Watanabe et al. 2017) v1.3.6 and were mapped to protein-coding genes using MAGMA v1.08. We applied a Bonferroni multiple testing correction that was defined as 0.05/(total number of genes in shared regions).

Causal genes present on shared loci across traits were further tested against eQTL data from the peripheral blood of 2,765 individuals from the Consortium for the Architecture of Gene Expression (Lloyd-Jones et al. 2017) and brain tissue of 449 individuals from the GTEx consortium (GTEx Consortium et al. 2017) using summary-data-based Mendelian Randomization (SMR), a method commonly used to identify the association between gene expression and complex traits using GWAS summary statistics (Zhu et al. 2016). We used a Bonferroni correction for multiple testing (0.05/total number of genes).

Human gene expression

Genes identified through functional annotation and a causal association between FTD and brain morphology in SMR were tested using the Allen Brain Atlas, which comprises an extensive dataset that links gene expression with neuroanatomical information (Sunkin et al. 2013). We used the brain model of a 57-year-old male, given that it is the model with the most similar age to the mean age in the UK Biobank (56.5 years) and the onset age for FTD (between 40 and 65 years). To accurately estimate differences in gene expression between males and females and between different ethnic groups, we conducted a chi-squared homogeneity test that included the gene expression for N-ethylmaleimide sensitive factor (NSF) in 39 regions of the brain from 5 male individuals between the ages of 24 and 57, 2 white Europeans, 2 African Americans, and 1 female of 49 years with a Hispanic ethnicity (see Supplementary Table 2). Nine brain regions with missing expression data were excluded from the analysis. We ran 2 separate models to test the homogeneity of NSF expression among different ethnic groups and between males and females. The first model included 3 categorical variables for ethnicity (i.e. Hispanic, White European, and African American), and the second model included 2 categories for sex (male or female). In instances where >1 measurement was present for a category, the mean estimate was included in the analysis. The Allen Brain Atlas project quantifies gene expression by fragment counts of RNA-Seq in a quantitative PCR; values are based on fluorescence or intensity measurements obtained from RNA microarrays. Results were based on probe number 1053553.

Mouse gene expression

To better understand the dynamics of the candidate FTD genes in both healthy aging and FTD, we compared expression from selected in a transgenic mouse model of tauopathy against wild-type (WT) mice. We utilized data from the Mouseac project, which includes brain tissue samples from the P301L-tau transgenic mouse model of FTLD (Hutton et al. 1998; Terwel et al. 2005) and WT mice of the same background strain at varying ages. The Mouseac project has been described in detail elsewhere (Matarin et al. 2015). Briefly, samples were collected from 3 brain

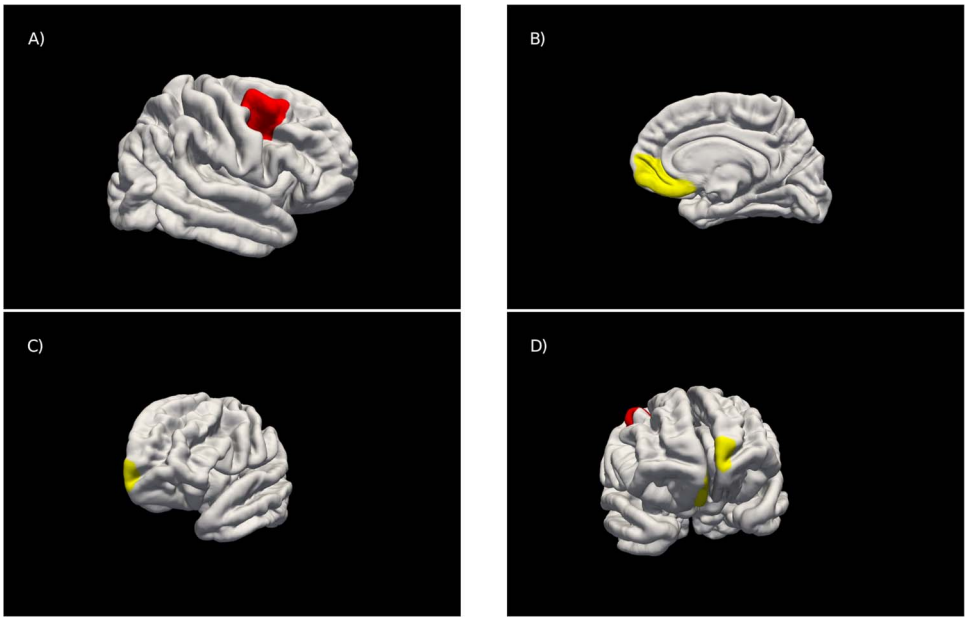

Fig. 1. Brain regions used in the GWAS-pairwise analyses. A) Lateral image of the right hemisphere highlighting the caudal middle frontal region in red, B) internal image of the right hemisphere highlighting the medial orbitofrontal in yellow, C) fronto-lateral image of the brain highlighting the frontal pole region in yellow, and D) frontal image of the brain with the frontal pole and medial orbitofrontal in yellow and the caudal middle frontal region in red.

regions (cortex, hippocampus, and cerebellum) from WT and P301L-tau transgenic mice at ages 8, 16, 32, and 72 weeks. Gene expression was measured using the Illumina Ref8 v2 microarray and was processed by the Mouseac project staff according to previously described and validated techniques (Matarin et al. 2015). Briefly, raw expression levels were normalized using a log2 transformation, and quantile normalization was performed for all samples. An individual probe was excluded if the *P*-value for detection was >0.05 in >50% of the WT and transgenic group's samples at any age. Additionally, samples were excluded if <95% of the probes for a given gene were detected. Tau pathology was quantified histologically (Matarin et al. 2015). Expression data were inspected for outlier data points and normality. ANOVA was used to test for gene expression differences between the P301L-tau transgenic mouse model and WT mice brain tissue with respect to both ages across all brain regions.

Results

LDSC genetic correlation

To elucidate the genetic factors influencing FTD risk and brain structure (Mufford et al. 2017), first we performed LD score regression and estimated pairwise genetic correlations (Supplementary Table 1). We did not observe any statistically significant genetic correlations between FTD and brain morphology measurements; this is most likely due to the limited sample size of the FTD GWAS. However, 4 brain MRI measurements were highly correlated with FTD ($r_g > 0.45$). For instance, the left frontal pole area ($r_g = 0.62$, s.e. = 0.41), right inferior parietal area ($r_g = 0.52$, s.e. = 0.27), right caudal middle frontal thickness ($r_g = 0.48$, s.e. = 0.27), and right medial orbitofrontal thickness ($r_g = 0.45$, s.e. = 0.32), as shown in Fig. 1.

GWAS-Pairwise

We further investigated the overlap between highly correlated brain regions with FTD ($r_g > 0.45$). We identified the region chr17:43057141–45874715 (GRCh37-hg19) as shared between FTD and 2 brain phenotypes, the right inferior parietal surface area, and the right medial orbitofrontal cortical thickness.

Functional annotation and eQTL

We mapped the SNPs in the region 43057141 to 45874715 on chromosome 17 for the right inferior parietal area, right medial orbitofrontal thickness, and FTD. Eight protein-coding genes (*ARMGAP27*, *CRHR1*, *KANSL1*, *NSF*, *PLEKHM1*, *SPPL2C*, *STH*, and *WNT3*) were shared between the 2 brain regions and FTD; however, these genes were only nominally significant after multiple testing correction. Results from SMR using peripheral blood eQTL data confirmed a common causal association between *NSF* expression, the right inferior parietal area ($b = 0.11$, s.e. = 0.03), right medial orbitofrontal thickness ($b = -0.19$, s.e. =0.04), and FTD ($b = -0.61$, s.e. = 0.21) (Fig. 2). Results from brain tissue eQTL data were inconclusive, given the small sample size ($n = 449$). *NSF* is a protein-coding gene in chromosome 17, which is highly expressed in brain tissue as compared to other tissues (Fan et al. 2020) and has been previously associated with red cell distribution, hemoglobin levels, balding, brain morphology, Parkinson's disease, blood pressure, and developmental and epileptic encephalopathy, among other traits (Belluzzi et al. 2016).

Human gene expression

Results regarding gene expression in the Allen Brain Atlas confirm the expression of *NSF* in the inferior parietal area and a medial orbitofrontal with a mean expression value of 12.8 and 12.7, respectively. The results of chi-squared tests of homogeneity showed no statistically significant differences in gene expression between ethnic groups or between males and females ($P > 0.05$). This suggests that there are no major variations in gene expression between the different groups. However, the data available are not a representative sample of the overall population, and further research is necessary to determine if these results are consistent under a larger sample size.

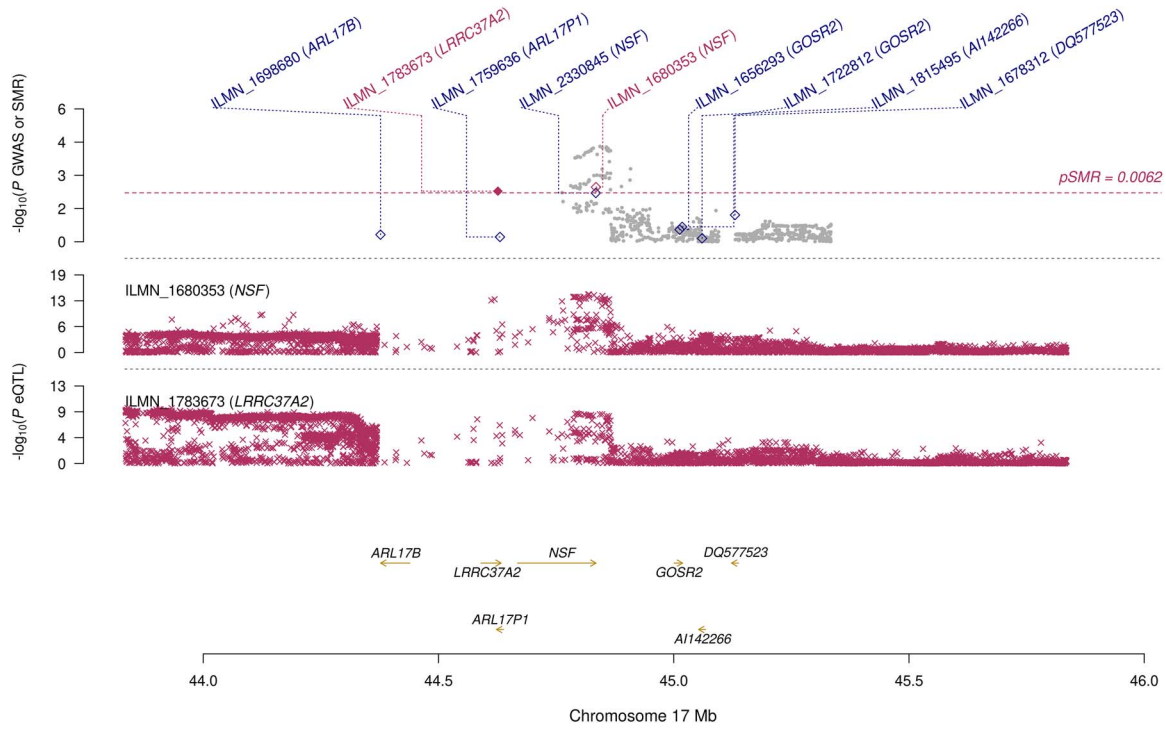

Fig. 2. Causal association between NSF and FTD based on eQTL data of peripheral blood. *P*-value corrected threshold (pSMR) = 0.0062.

Mouse gene expression

To further characterize and explore the above-described findings in humans, we next used gene expression data from P301L transgenic and WT mice to explore the relationships between *NSF* and *MAPT* expression at varying ages across the brain. We started by comparing the main effects of a brain region, age, and transgene status. ANOVA analyses revealed significant differences in *NSF* ($P = 1.96E-04$**)** and *MAPT* ($P = 0.01$) expression in P301L transgenic mice relative to WT mice when compared by brain region across age (Table 1). Given this, we next explored the expression of *NSF* and *MAPT* within the cortex, hippocampus, and cerebellum to characterize the expression changes across time within each brain region that were driving our findings. Interestingly, *NSF* ($P = 4.68E-04$), but not *MAPT* ($P > 0.05$), demonstrated significantly different expression over time in P301L mice relative to WT mice despite increasing tau pathology in the cerebral cortex (Fig. 3A–C). In the hippocampus, both *NSF* ($P = 4.72E-04$) and *MAPT* ($P = 1.56E-05$) expression decreased over time in P301L mice relative to WT mice as tau pathology increased (Fig. 3D–F). Finally, in the cerebellum, there was no temporal relationship between *NSF* ($P > 0.05$) and *MAPT* ($P > 0.05$) expression in P301L mice relative to WT mice(Fig. 3G and H), and there was no significant burden of tau pathology in this region (Fig. 3I).

Discussion

In this work, we sought to advance our understanding of the genetic and molecular underpinnings of the relationship between FTD and brain morphology. We conducted LD score regression and GWAS-PW analyses. We identified 1 shared genomic region in chromosome 17 between FTD risk and 2 brain regions (right inferior parietal surface area and right medial orbitofrontal cortical thickness). In addition, we provide evidence for a putative causal association between brain morphology, FTD, and the *NSF* gene.

We note that although the genetic correlations between brain morphology and FTD did not reach statistical significance, they do not necessarily indicate a lack of an association between these phenotypes, especially when considering the high correlation values between FTD, the small sample size of FTD, and brain structural measurements in the frontal and parietal regions. This claim is supported by the significant correlation of the parietal and orbitofrontal brain regions with FTD through GWAS-PW.

Studies seeking to investigate behavioral changes in FTD have demonstrated the crucial role of the orbitofrontal cortex in the determination of social and emotional behavior (Viskontas et al. 2007). Individuals with lesions in the orbitofrontal cortex have shown impairment, to different extents, of stimulus–reward reversal learning, response inhibition, and the ability to judge the appropriateness of their social behavior (Viskontas et al. 2007). In addition, individuals with progressive atrophy in the orbitofrontal cortex experience detriment in emotion recognition, empathy, and their capacity to process complex stimulus–reward contingencies (Viskontas et al. 2007). It has been suggested that the substantial (50%–75%) and selective loss of Von Economo neurons, which is not as prominent among other types of dementia, could be an early major event shaping the manifestation of FTD symptoms (Viskontas et al. 2007; Santillo et al. 2013). Therefore, measurements of the orbitofrontal cortex have been proposed to discriminate between subtypes of FTD (Hornberger et al. 2010).

Similarly, neuroimaging studies have suggested that atrophy in the inferior parietal lobe, which is associated with anosognosia and mild cognitive impairment (Sedaghat et al. 2008), could be a potential marker for the diagnosis of Alzheimer's disease (AD) (Jacobs et al. 2011). In addition, previous studies have linked metabolic dysfunctions in the inferior parietal area with reduced autonoetic consciousness in FTD (Muñoz et al. 2019).

We identified a common potential causal association between *NSF* and FTD and between *NSF* and 2 brain morphological measurements (the right inferior parietal area and right medial

Table 1. ANOVA results from the tau P301L mouse model of frontotemporal lobar degeneration are shown when compared by transgene status, age, and brain region (cortex, hippocampus, or cerebellum). Significant findings (*P*-value < 0.05) are shown in bold. Data used in these analyses were obtained from the Mouseac Project (http://www.mouseac.org/) (Matarin et al. 2015).

	Gene	P301L	Age	Region	P301L:age	P301L:region	Age:region	P301L: Age:region
Across brain regions	*NSF*	0.83	0.67	**<2E-16**	**0.04**	0.11	0.15	**1.96E-04**
	MAPT	0.55	0.11	**5.18E-04**	**2.83E-03**	0.97	0.28	**0.01**
Within cortex	*NSF*	0.93	0.77	-	**4.68E-04**	-	-	-
	MAPT	0.78	0.76	-	0.48	-	-	-
Within hippocampus	*NSF*	0.07	0.07	-	**4.72E-04**	-	-	-
	MAPT	0.82	**0.04**	-	**1.56E-05**	-	-	-
Within cerebellum	*NSF*	0.36	0.42	-	0.10	-	-	-
	MAPT	0.62	0.26	-	0.80	-	-	-

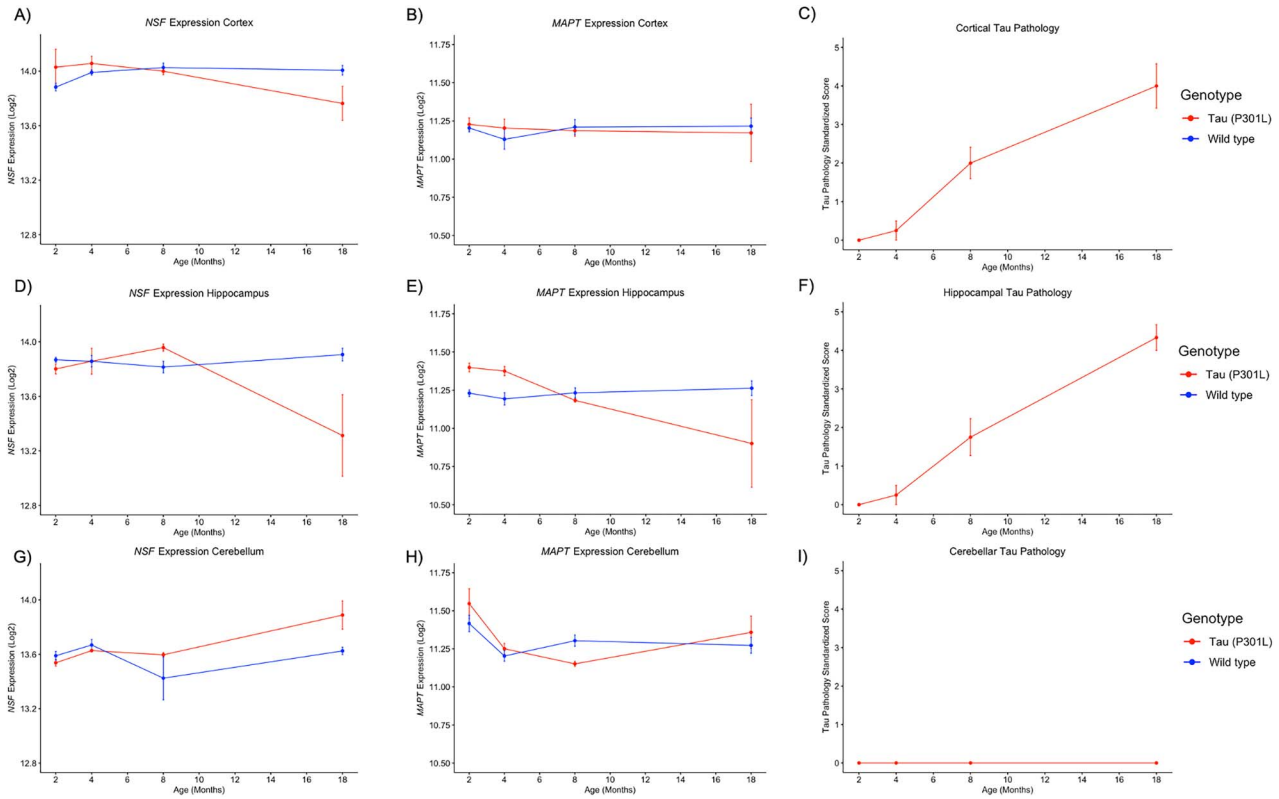

Fig. 3. *NSF* and *MAPT* expression in both pathologic and normal aging. Line plots with mean expression at each time point (+/− the standard error) for *NSF* and *MAPT* expression in the P301L mouse model of FTD relative to WT mice across the lifespan (data courtesy of the Mouseac Project, http://www.mouseac.org/) (Matarin et al. 2015). Expression profiles are shown for *NSF* and *MAPT* by brain region with across multiple ages stratified by transgene status. A and B) In the cortex, there was a significant association between *NSF* expression ($P = 4.68E-04$) and P301L transgene status over time which was not observed in *MAPT* ($P > 0.05$). C) Accumulation of tau pathology at varying ages in the cortex is provided as a reference. D and E) By contrast, in the hippocampus, both *NSF* ($P = 4.72E-04$) and *MAPT* ($P = 1.56E-05$) expression was significantly different in P301L transgenic mice relative to controls at varying ages when compared to WT. F) Accumulation of tau pathology at different ages in the hippocampus is provided as a reference. Finally, no association was observed for NSF ($P > 0.05$) or MAPT ($P > 0.05$) expression across time when comparing P301L transgenic mice relative to controls. I) Neither P301L nor WT mice demonstrate significant tau pathology at any age.

orbitofrontal thickness). *NSF* is a protein-coding gene that has been associated with protein kinase binding (Belluzzi et al. 2016) which in turn contributes to adaptive homeostasis mechanisms working as signaling pathways of the cellular response to stress (Pomatto and Davies 2017). Notably, a decrease in the signaling through the kinase sensor mechanisms has been associated with age-related neurodegeneration (Martinez et al. 2021). *NSF* has also been associated with AD (Fan et al. 2020) and Parkinson's disease (Cheng et al. 2020; Fan et al. 2020) and FTD, as per the results of this study. However, NSF expression has been associated with *MAPT* haplotype (Soto-Beasley et al. 2020). We further assessed the expression of *MAPT* through eQTL of brain tissue with inconclusive results due to a low sample size ($n = 449$). Therefore, it is unclear if there is a causal association between *MAPT* and FTD and the degree in which NSF expression in brain tissue could be related to *MAPT*.

Gene expression data in the brain atlas confirmed the expression of *NSF* in the inferior parietal and medial orbitofrontal regions. That suggests an underlying biological mechanism between neurodegenerative conditions which may affect specific brain regions. Studies investigating the role of *NSF* in the etiology of tauopathies report that a reduction in *NSF* expression levels

reflects extensive neurodegeneration in the brain (Mackenzie et al. 2006).

Furthermore, genetic studies have demonstrated that the *NSF*/rs199533 minor allele is protective against AD risk, and its homozygosity has been shown to delay the age at onset of AD (Fan et al. 2020), which comes in contrast with its role in the etiology of PD where it increases risk for the disease (Fan et al. 2020). Building upon these findings, we show in a mouse model of frontotemporal lobar degeneration that cortical *NSF*, but not *MAPT*, expression decreases with increasing age—corresponding closely with the steadily increasing burden of tau pathology in the cortex. These findings may help to elucidate how *NSF* expression changes uniquely contribute to risk for and the pathophysiology of frontotemporal lobar degeneration independent of its association with the *MAPT* locus.

We must acknowledge several limitations of this study. For instance, the small sample size for FTD used in the present study resulted in low statistical power, which was further limited by strict multiple testing corrections. Therefore, we note that a nonsignificant association in this study does not necessarily reflect a lack of association.

Similarly, eQTL data also had a constrained sample size. Future studies should leverage larger sample sizes to unveil other potential causal associations between specific genes, brain morphology, and FTD. In addition, GWAS data used here represent individuals of European ancestry. Results should not be generalized to other populations until findings are confirmed using data for different ancestry populations.

Our results highlight a genetic correlation between FTD risk and brain structure (right inferior parietal surface area and right medial orbitofrontal cortical thickness) at the genome-wide level and implicate the *NSF* gene in the etiology of FTD. This study advances our understanding of the relationship between FTD, brain morphology, and genetic factors despite the relatively modest sample size of the existing FTD GWAS. Further research is required to elucidate further the role of the *NSF* gene in the etiology of FTD and whether it could be targeted in neuroprotective treatments.

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Authors' contributions

Santiago Diaz-Torres (Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing—original draft), Natalia Ogonowski (Data curation, Investigation, Methodology, Writing—original draft, Writing—review & editing), Luis M. García-Marín (Formal analysis, Software, Writing—review & editing), Luke W. Bonham (Formal analysis, Methodology, Writing—review & editing), Claudia Duran-Aniotz (Conceptualization, Writing—review & editing), Jennifer S. Yokoyama (Conceptualization, Methodology, Writing—review & editing), and Miguel E. Rentería (Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing—review & editing)

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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Conflict of interest statement: None declared.

Data availability

Data and code associated with this study may be made available upon request to the authors.

Ethics declaration

This study used summary-based statistics from GWAS. Ethics approval for individual studies is described in the original publications where the GWAS are described.

Consent to participate

No individual-based data were used in this study. Participants in all cohorts from these studies gave written informed consent, and the sites involved obtained approval from local research ethics committees or Institutional Review Boards.

Consent for publication

Not applicable.

Competing interests

JSY serves in the scientific advisory board for the Epstein Family Alzheimer's Research Collaboration. All remaining authors declare no competing interests.

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