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Selective Genetic Overlap Between Amyotrophic Lateral Sclerosis and Diseases of the Frontotemporal Dementia Spectrum

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IMPORTANCE Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by loss of upper and lower motor neurons. Although novel ALS genetic variants have been identified, the shared genetic risk between ALS and other neurodegenerative disorders remains poorly understood.

OBJECTIVES To examine whether there are common genetic variants that determine the risk for ALS and other neurodegenerative diseases and to identify their functional pathways.

DESIGN, SETTING, AND PARTICIPANTS In this study conducted from December 1, 2016, to August 1, 2017, the genetic overlap between ALS, sporadic frontotemporal dementia (FTD), FTD with TDP-43 inclusions, Parkinson disease (PD), Alzheimer disease (AD), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP) were systematically investigated in 124 876 cases and controls. No participants were excluded from this study. Diagnoses were established using consensus criteria.

MAIN OUTCOMES AND MEASURES The primary outcomes were a list of novel loci and their functional pathways in ALS, FTD, PSP, and ALS mouse models.

RESULTS Among 124 876 cases and controls, genome-wide conjunction analyses of ALS, FTD, PD, AD, CBD, and PSP revealed significant genetic overlap between ALS and FTD at known ALS loci: rs13302855 and rs3849942 (nearest gene, *C9orf72*; $P = .03$ for rs13302855 and $P = .005$ for rs3849942) and rs4239633 (nearest gene, *UNC13A*; $P = .03$). Significant genetic overlap was also found between ALS and PSP at rs7224296, which tags the *MAPT* H1 haplotype (nearest gene, *NSF*; $P = .045$). Shared risk genes were enriched for pathways involving neuronal function and development. At a conditional FDR $P < .05$, 22 novel ALS polymorphisms were found, including rs538622 (nearest gene, *ERGIC1*; $P = .03$ for ALS and FTD), which modifies *BNIP1* expression in human brains (35 of 137 females; mean age, 59 years; $P = .001$). *BNIP1* expression was significantly reduced in spinal cord motor neurons from patients with ALS (4 controls: mean age, 60.5 years, mean [SE] value, 3984 [760.8] arbitrary units [AU]; 7 patients with ALS: mean age, 56 years, mean [SE] value, 1999 [274.1] AU; $P = .02$), in an ALS mouse model (mean [SE] value, 13.75 [0.09] AU for 2 *SOD1* WT mice and 11.45 [0.03] AU for 2 *SOD1* G93A mice; $P = .002$) and in brains of patients with PSP (80 controls: 39 females; mean age, 82 years, mean [SE] value, 6.8 [0.2] AU; 84 patients with PSP: 33 females, mean age 74 years, mean [SE] value, 6.8 [0.1] AU; $\beta = -0.19$; $P = .009$) or FTD (11 controls: 4 females; mean age, 67 years; mean [SE] value, 6.74 [0.05] AU; 17 patients with FTD: 10 females; mean age, 69 years; mean [SE] value, 6.53 [0.04] AU; $P = .005$).

CONCLUSIONS AND RELEVANCE This study found novel genetic overlap between ALS and diseases of the FTD spectrum, that the *MAPT* H1 haplotype confers risk for ALS, and identified the mitophagy-associated, proapoptotic protein *BNIP1* as an ALS risk gene. Together, these findings suggest that sporadic ALS may represent a selectively pleiotropic, polygenic disorder.

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Supplemental content

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are thought to represent a continuous disease spectrum.[1] Clinically, ALS presents as progressive muscle wasting, hyperreflexia, and spasticity, whereas FTD is defined by cognitive and behavioral dysfunction. Between 40% and 50% of patients with ALS present with FTD-associated clinical phenotypes, including progressive aphasia, language impairment, and executive dysfunction.[1] Neuropathologically, ALS is defined by the loss of upper and lower motor neurons and the formation of TDP-43, SOD1, and ubiquitin-positive inclusions within motor neurons. Frontotemporal dementia is defined by atrophy of the frontal and temporal lobes, and subtypes of FTD are distinguished by the types of inclusions in these regions (tau, FUS, TDP-43, and ubiquitin).[2] Comparatively less is known about the shared pathobiology between ALS and other neurodegenerative diseases, such as Alzheimer disease (AD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and Parkinson disease (PD).

Genetic factors offer insights into the molecular mechanisms underlying disease. Rare mutations in *TDP43* (GenBank 3435) are associated with ALS and FTD.[3-5] Genetic studies have revealed expansions of the hexanucleotide repeat within the noncoding promoter region of *C9orf72* (GenBank 203228) as the cause of ALS and FTD.[6,7] However, beyond *C9orf72* and *TDP43*, the genetic overlap across sporadic forms of ALS, FTD, and other neurodegenerative diseases remains poorly understood.

One approach to assessing additional genetic risk among these diseases is to identify single-nucleotide polymorphisms (SNPs) that are jointly associated with multiple traits.[8-11] Using previously validated methods, we investigated the genetic overlap between ALS, FTD, PSP, CBD, AD, and PD. We then used molecular and bioinformatics approaches to begin to define the role that these shared risk genes play in neurodegeneration.

Key Points

Question Are there genome-wide genetic risk factors for amyotrophic lateral sclerosis that are shared with other neurodegenerative diseases?

Findings This study of combined genome-wide association data identified selective genetic overlap between amyotrophic lateral sclerosis and neurodegenerative diseases within the frontotemporal dementia spectrum.

Meaning These findings identify common genetic pathways between amyotrophic lateral sclerosis and frontotemporal dementia and suggest that *MAPT* and *BNIP1* influence the pathogenesis of amyotrophic lateral sclerosis.

Methods

Participant Samples

We evaluated summary statistics (*P* values and odds ratios) from genome-wide association studies (GWASs) for ALS, PD, AD, CBD, PSP, sporadic FTD, and autosomal dominant FTD with TDP-43 inclusions (eTable 1 in the Supplement). The GWASs were performed for individuals of European descent. Samples have been previously described in detail.[12-18] The data set on ALS represents 31 independent cohorts of participants with ALS and control participants.[14] Amyotrophic lateral sclerosis was diagnosed as probable or definite according to the 1994 El Escorial Criteria by neurologists specializing in motor neuron diseases.[19] The data set on sporadic FTD included multiple subtypes within the FTD spectrum: behavioral variant FTD, semantic dementia, progressive nonfluent aphasia, and FTD overlapping with motor neuron disease. The relevant institutional review boards or ethics committees approved the research protocol of the individual GWASs used in the present analysis, and all human participants gave written informed consent. The Human Research Protection Program Institutional Review Board at University of California San Francisco waived consent for all participants. The Institutional Review Board determined that the use or disclosure of the information does not adversely affect the rights and welfare of the individuals and involves no more than a minimal risk to their privacy.

Statistical Analysis

Genetic Enrichment

We applied previously validated statistical methods to assess shared genetic risk and identify ALS susceptibility loci.[9,10,20-22] We evaluated SNPs associated with increased risk for ALS and FTD, ALS and PD, ALS and AD, ALS and CBD, ALS and PSP, and ALS and FTD with TDP-43 inclusions. Using this approach, the genetic enrichment of phenotype A with phenotype B exists if the proportion of SNPs or genes associated with phenotype A increases as a function of the increased association with phenotype B. To evaluate enrichment, we constructed fold-enrichment and quantile-quantile plots of nominal $-\log_{10}$ *P* values for all ALS SNPs and for subsets of SNPs determined by the significance of their association with PD, AD, CBD, PSP, and FTD (sporadic FTD and FTD with TDP-43 inclusions) (eFigure 1 in the Supplement). Enrichment can be directly interpreted in terms of the true discovery rate, which is equal to 1 minus the false discovery rate (FDR) (eAppendix 1 in the Supplement).[9,10,20-22] To minimize false positives, we used a 100-iteration random pruning with a linkage disequilibrium (LD) $r^2 < 0.2$.[21]

Identification of Shared Risk Loci-Conjunction FDR

To identify specific loci jointly shared between ALS and PD, AD, CBD, PSP, or FTD (sporadic FTD and FTD with TDP-43 inclusions), we computed the conjunction FDR.[8,9,20,21] The conjunction FDR is defined as the posterior probability that an SNP is null for either phenotype or for both simultaneously, given that the *P* values for both traits are as small, or smaller, than the *P* values for each trait individually (eAppendix 1 in the Supplement).[8,9] We used an overall FDR threshold of $P < .05$ to indicate statistical significance. Manhattan plots were constructed based on the ranking of the

conjunction FDR to illustrate the genomic location of the shared genetic risk loci.

Identification of Novel Risk Loci-Conditional FDR

To identify specific ALS susceptibility loci as a function of genetic variants associated with the 6 neurodegenerative disorders, we computed conditional FDRs.[20,21] The conditional FDR is an extension of the standard FDR, which incorporates information from GWAS summary statistics of a second phenotype to adjust its significance level. The conditional FDR is defined as the probability that an SNP is null in the first phenotype given that the *P* values in the first and second phenotypes are as small as or smaller than the observed ones. Ranking SNPs by the standard FDR or by *P* values gives the same ordering of SNPs. In contrast, if the primary and secondary phenotypes are related genetically, the conditional FDR reorders SNPs and results in a different ranking than that based on *P* values alone. We used an overall FDR threshold of $P < .05$ to indicate statistical significance, which means 5 expected false discoveries per 100 reported. In addition, we constructed Manhattan plots based on the ranking of the conditional FDR to illustrate the genomic location. In all analyses, we controlled for the effects of genomic inflation by using intergenic SNPs (eAppendix 1 in the Supplement). Detailed information on the conditional FDR can be found in prior reports.[20,21]

Functional Evaluation of Shared Risk Loci

To determine whether the conjunction and conditional SNPs shared across ALS, PD, AD, CBD, PSP, and FTD (sporadic FTD and FTD with TDP-43 inclusions) modify gene expression, we evaluated *cis*-expression quantitative trait loci (eQTL) in a publicly available data set from neuropathologically confirmed control brains (UK Brain Expression Consortium, http://braineac.org/).[23] To minimize multiple comparisons, we analyzed eQTL for the mean *P* value derived across the following brain regions: the cerebellum, frontal cortex, hippocampus, medulla, occipital cortex, putamen, substantia nigra, temporal cortex, thalamus, and white matter. To minimize false positives, we applied a Bonferroni-corrected *P* value of 1.5×10^{-3}. To test for association between genotypes and gene expression, we used an analysis of covariance. We tested SNPs using an additive model in SAS (SAS Institute Inc). To evaluate *cis*-acting splicing quantitative trait loci (sQTL), we examined the associations of our shared risk SNPs with alternative splicing in control human brains.[24] Each study reported genetic and expression data on brains from individuals of European descent.

Differential Expression of Shared Genetic Risk Variants in Tissues of Patients With ALS, PSP, FTD, AD, or PD

To determine whether shared risk genes identified by the conjunction FDR, the conditional FDR, and genes in *cis*-eQTL were differentially expressed in tissue from patients with ALS compared with controls, we analyzed the gene expression of the target genes in motor neurons isolated from 11 patients with ALS and controls (Gene Expression Omnibus [GEO] accession number GSE833).[25] To validate the genes identified in GSE833, we examined expression data from a well-characterized mouse model.[26] The RNA expression data were analyzed in nontransgenic *SOD1* WT and *SOD1* G93A mice at 75 and 110 days (GEO accession number GSE4390).[27] *SOD1* G93A mice are presymptomatic at 75 days and exhibit hindlimb paralysis at 110 days.[26,27]

To determine whether differentially expressed genes in ALS were altered across brains with neurodegenerative disease, we analyzed the gene expression of the target genes using publicly available data sets. Differential gene expression was analyzed from the following data sets: the temporal cortices from patients with PSP and control brains (Synapse ID No. syn6090802)[28] and the frontal, hippocampus, and cerebellum from patients with FTD and controls (GEO accession number E13162).[29] Each data set of control and disease tissue was obtained from individuals of European descent. All analyses were performed using analysis of covariance in SAS.

Gene Ontologic Features and Network-Based Functional Association Analyses

To identify enrichments in gene ontologic features associated with the ALS, PD, AD, CBD, PSP, and FTD (sporadic FTD and FTD with TDP-43 inclusions) shared risk genes identified by the conjunction FDR, the conditional FDR, and genes in *cis*-eQTL, we used the Consensus Path Database, which compares gene ontologic terms between background and candidate gene sets using the hypergeometric test and generates *P* values that are corrected for multiple testing using the FDR. Gene ontologic analyses were performed using the Consensus Path Database (Release 31; http://cpdb.molgen.mpg.de/).[30,31] We used the default background gene set, which includes 18 043 genes. Biological, cellular, and molecular gene ontologic terms were included in a single analysis.

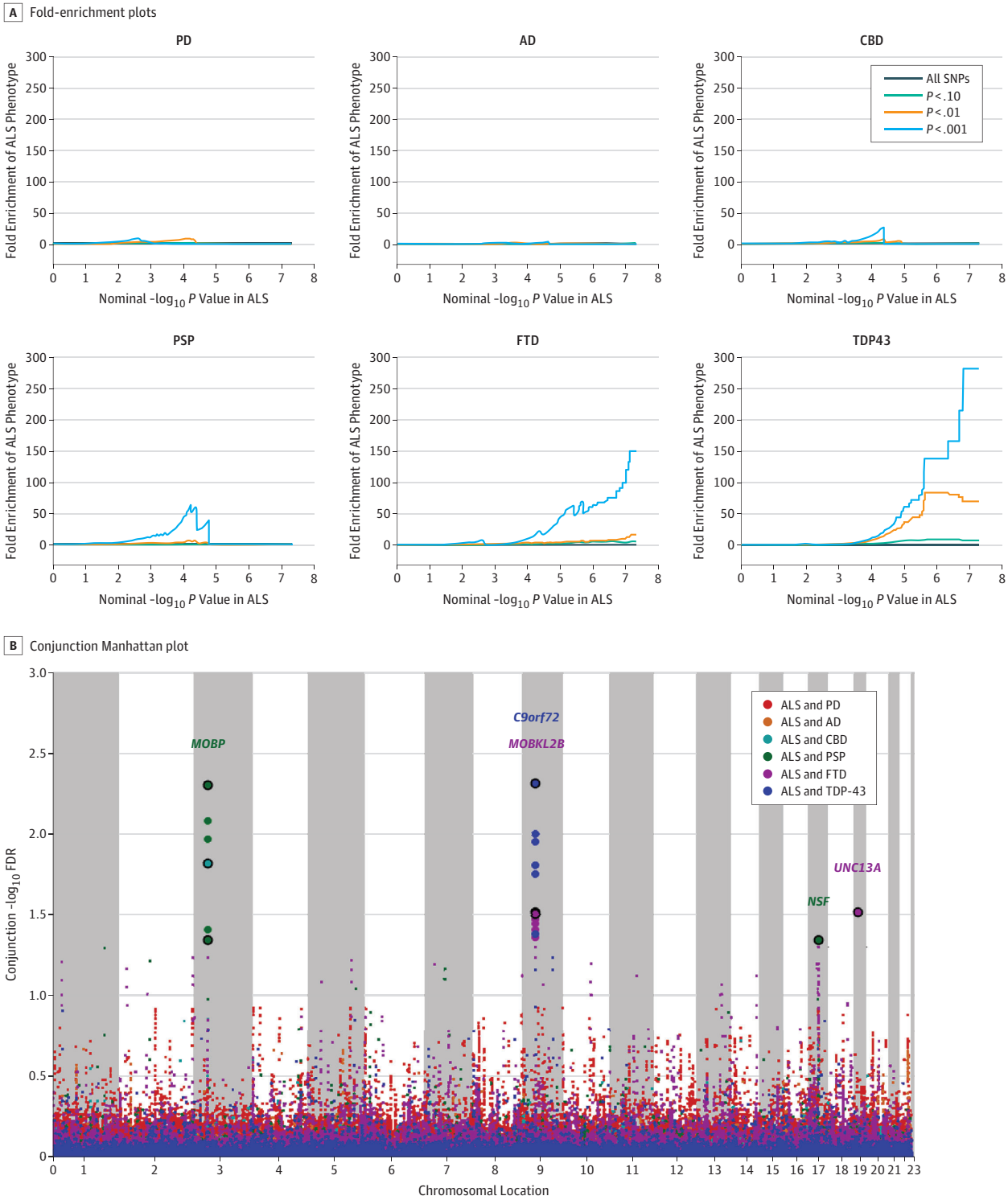
Results

Selective Shared Genetic Risk Between ALS, PD, AD, CBD, PSP, and FTD

We identified enrichment in ALS SNPs across different levels of significance with FTD, PSP, and CBD (**Figure 1**). Applying progressively stringent *P* value thresholds for ALS SNPs (ie, increasing values of nominal $-\log_{10} P$ value), we found up to 300-fold enrichment using FTD with TDP-43 inclusions, 150-fold enrichment using FTD, 75-fold enrichment using PSP, and 25-fold enrichment using CBD (Figure 1). In contrast, we found minimal or no enrichment in ALS SNPs as a function of AD or PD (Figure 1).

At a conjunction FDR $P < .05$, we identified 5 SNPs that were jointly associated with increased risk for ALS and FTD with TDP-43 inclusions, ALS and FTD, or ALS and PSP (Figure 1 and **Table 1**). These SNPs included the following: (1) rs9820623 (nearest gene, *MOBP* [GenBank 17433]; FDR ALS and PSP, $P = 4.99 \times 10^{-3}$); (2) rs13302855 (nearest gene, *C9orf72*; FDR ALS and FTD, $P = 3.13 \times 10^{-2}$); (3) rs3849942 (nearest gene, *C9orf72*; FDR ALS and FTD with TDP-43 inclusions, $P = 4.88 \times 10^{-3}$); (4) rs7224296 (nearest gene, *NSF* [GenBank 4905]; FDR ALS and PSP, $P = 4.52 \times 10^{-2}$); (5) rs4239633 (nearest gene, *UNC13A* [GenBank 23025]; FDR ALS and FTD, $P = 3.05 \times 10^{-2}$).

Figure 1. Genetic Enrichment Across the Amyotrophic Lateral Sclerosis (ALS)–Frontotemporal Dementia (FTD) Spectrum



A, Fold-enrichment plots. Graphs depict enrichment vs nominal $-\log_{10} P$ values (corrected for inflation) in amyotrophic lateral sclerosis (ALS) below the standard genome-wide association study threshold of $P < 5 \times 10^{-8}$ as a function of significance of association with Parkinson disease (PD), Alzheimer disease (AD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), frontotemporal dementia (FTD) (sporadic and FTD with TDP-43 inclusions [TDP43]) and at the level of $-\log_{10} P \geq 0$ corresponding to $-\log_{10} P \leq 1$, $-\log_{10} P \geq 1$ corresponding to $P \leq .10$, and $-\log_{10} P \geq 2$ corresponding to $P \leq .01$. B, Conjunction Manhattan plot showing shared risk loci. A plot of conjunction $-\log_{10}$ (false discovery rate [FDR]) values for ALS given PSP, CBD, TDP-43, and FTD. Single-nucleotide polymorphisms (SNPs) with conjunction $-\log_{10}$ FDR > 1.3 (ie, FDR $P < .05$) are shown as large points. A black line around the large points indicates the most significant SNP in each linkage disequilibrium block. This SNP was annotated with the nearest gene, which is listed above the symbols in each locus.

Table 1. Shared Risk SNPs Between ALS and FTD, PSP, CBD, TDP43, AD, and PD at a Conjunction FDR < 0.05

SNP	Chr	Nearest Gene	Associated Phenotype	Minimum Conjunction FDR	ALS *P* Value
rs9820623	3	*MOBP*	PSP	4.99×10^{-3}	1.69×10^{-5}
rs13302855	9	*C9orf72*	FTD	3.13×10^{-2}	4.04×10^{-6}
rs3849942	9	*C9orf72*	TDP43	4.88×10^{-3}	6.29×10^{-19}
rs7224296	17	*NSF*	PSP	4.54×10^{-2}	5.90×10^{-4}
rs4239633	19	*UNC13A*	FTD	3.05×10^{-2}	1.98×10^{-6}

Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; CBD, corticobasal degeneration; Chr, chromosome; FDR, false discovery rate; FTD, frontotemporal dementia; PD, Parkinson disease; PSP, progressive supranuclear palsy; SNP, single-nucleotide polymorphism; TDP43, FTD with TDP-43 inclusions.

Table 2. eQTL That Reveal Functional Effects of Shared Risk SNPs in a Human Brain Tissue (UK Brain Expression Consortium)

			eQTL	
SNP	Chr	Nearest Gene	*P* Value	Gene
rs9820623	3	*MOBP*	4.40×10^{-3}	*SCN11A*
rs13302855	9	*C9orf72*	1.30×10^{-2}	*LRRC19*
rs3849942	9	*C9orf72*	4.80×10^{-3}	*MOBKL2B*
rs7224296	17	*NSF*	3.30×10^{-18}	*KIAA1267*
			6.5×10^{-5}	*MAPT*
			6.9×10^{-11}	*MAPT* exon 3
rs4239633	19	*UNC13A*	1.00×10^{-3}	*ELL*

Abbreviations: Chr, chromosome; eQTL, *cis*-expression quantitative trait loci; SNP, single-nucleotide polymorphism.

Conditional FDR Analysis and Novel Risk Loci

Conditional FDR analysis revealed 29 additional risk loci at an FDR $P < .05$ (eFigure 1 and eTable 2 in the Supplement). Signals at rs3849943, rs10511816, and rs13302855 (nearest gene, *C9orf72*; rs3849943: FDR for ALS and FTD, $P = 5.30 \times 10^{-9}$, ALS $P = 4.56 \times 10^{-19}$; rs10511816: FDR for ALS and FTD, $P = 4.97 \times 10^{-9}$, ALS $P = 6.08 \times 10^{-11}$; rs13302855: FDR for ALS and FTD, $P = 2.03 \times 10^{-4}$; ALS $P = 4.04 \times 10^{-6}$); rs12608932 (nearest gene, *UNC13A*; FDR for ALS and FTD, $P = 1.04 \times 10^{-6}$; ALS $P = 1.83 \times 10^{-8}$); rs1768208 and rs13079368 (nearest gene, *MOBP*; rs1768208: FDR for ALS, FTD, and PSP, $P = 6.89 \times 10^{-3}$, ALS $P = 4.04 \times 10^{-5}$; rs13079368: FDR for ALS, FTD, and PSP, $P = 1.99 \times 10^{-3}$; ALS $P = 4.11 \times 10^{-5}$); and rs7813314 (nearest gene, *BC045738* [GenBank 101927815]; FDR for ALS and FTD, $P = 4.86 \times 10^{-3}$; ALS $P = 7.78 \times 10^{-7}$) have been described previously to be associated with ALS.[14] In addition, we identified 22 additional novel risk SNPs, including rs538622 (nearest gene, *ERGIC1* [GenBank 57222]; FDR for ALS and FTD, $P = 3.07 \times 10^{-2}$; ALS $P = 1.37 \times 10^{-5}$; eTable 2 in the Supplement). Among these novel risk SNPs, we identified rs7224296 (nearest gene, *NSF*), which is located on chromosome 17 and occurs within the 1-megabase (Mb) inversion of the *MAPT* (GenBank 4137) haplotype.

eQTL and sQTL

To begin to define the functional effects of these shared risk SNPs, we evaluated *cis*-eQTL in human brains free of neuropathologic characteristics (**Table 2**). The SNP rs7224296 near *NSF* has been previously reported to tag the *MAPT* H1 haplotype.[9] The *MAPT* H1 haplotype is associated with increased risk for FTD, PSP, CBD, AD, and PD.[10,11,13,16-18] However, the most significant *cis*-eQTL with 24296 occurred with *KIAA1267* (GenBank 284058) (also known as *KANSL1*) (Table 2). rs7224296 is in high LD with rs199533 ($D' = -0.97$), which was previously reported to be associated with shared risk for PSP, CBD, and FTD.[9] Consistent with previous findings for rs199533,[9] rs7224296 is significantly associated with the altered expression of exon 3 within the *MAPT* gene (Table 2). *MAPT* H1 is associated with decreased expression of messenger RNA transcripts containing exons 2 and 3, which results in the 2N tau protein.[32] Together, these findings point to an association between the *MAPT* H1 haplotype and the risk for ALS.

We also identified 2 SNPs sharing genetic overlap between ALS and FTD or ALS and FTD with TDP-43 inclusions near *C9orf72*: rs13302855 and rs3849942 (Table 1). These SNPs are not in LD ($r^2 < 0.02$). The SNP rs13302855 produced distinct eQTL with *LRRC19* (GenBank 64922), and rs3849942 produced distinct eQTL with *MOBKL2B* (GenBank 79817) (Table 2). Thus, our findings suggest that there are 2 independent signals within the *C9orf72* locus that confer risk. In addition to *cis*-eQTL, we examined the association of shared risk SNPs with sQTL. We found that rs2282241 (nearest gene, *C9orf72*; conditional FDR ALS and FTD with TDP-43 inclusions, $P = 3.68 \times 10^{-5}$; ALS $P = 1.55 \times 10^{-7}$) was significantly associated with alternative splicing of the *C9orf72* gene (alternative splicing ID, HsaINT0025532; FDR $P = 1.08 \times 10^{-3}$), specifically intron retention. The sQTL SNP rs2282241 is in high LD with rs3849942 ($D' = 0.99$; Table 1).

Among the novel ALS risk SNPs identified by conditional FDR analysis, we identified *cis*-eQTL in human brains (eTable 3 in the Supplement). Most ALS risk SNPs produced *cis*-eQTL with genes within the associated locus but not with the nearest named gene. We found that rs538622, which is associated with ALS and FTD and falls near the *ERGIC1* gene, is significantly associated with *BNIP1* (GenBank 662) such that the minor allele (*G*) is associated with the lower expression of *BNIP1* in human brains ($P = 1.1 \times 10^{-3}$).

Attenuation of Genetic Enrichment After Removing *C9orf72* and *MAPT*

We identified several SNPs in *C9orf72* (on chromosome 9) and in LD with *MAPT* (on chromosome 17), suggesting that variants associated with *C9orf72* and *MAPT* were critical in driving our enrichment results. To test this hypothesis, we repeated our enrichment analysis after removing all SNPs in LD with $r^2 > 0.2$ within 1 Mb of *C9orf72* and *MAPT* variants (based on 1000 Genomes Project[33] LD structure). After removing *C9orf72* and *MAPT* SNPs, we observed considerable attenuation of genetic enrichment in ALS as a function of FTD with TDP-43 inclusions (eFigure 2 in the Supplement). However, we still found robust enrichment between ALS and PSP (100-fold enrichment) and sporadic FTD (800-fold enrichment; eFigure 2 in the Supplement), suggesting that the observed overlap between ALS and FTD was not driven by the *C9orf72* and *MAPT* regions.

Shared Genetic Risk Genes Reveal Dysregulation of Neuronal Networks

To determine whether the shared risk genes fall within common biological pathways, we used bioinformatics approaches to identify common pathways. Because most risk SNPs occur within intergenic regions, we used 2 approaches to associate a risk SNP with a gene: genes nearest the SNPs and genes producing eQTL with the SNPs. Pathway analysis reveals that shared risk genes, from conjunction and conditional analyses, fall within pathways directly involved in neuronal function: axon guidance, myelin sheath, synaptic vesicle pathways, neuronal action potential, and regulation of postsynaptic membrane potential, among others (**Table 3**; eTables 4 and 5 in the Supplement).

Differential Expression of Shared Risk Genes in Tissues of Patients With ALS, FTD, PSP, AD, or PD

We next sought to determine whether the risk genes shared across ALS, FTD, PSP, and CBD were differentially expressed in disease tissues. To make this determination, we assessed the differential expression of the genes nearest the top SNP from conditional and conjunction FDR analyses and of the genes that produced the strongest eQTL in our functional analyses in motor neurons isolated from spinal cords of patients with ALS and controls (genes included in the analysis were taken from Tables 1 and 2 and from eTables 2 and 3 in the Supplement).[25] Only 15 genes fitting these criteria were present in the ALS data set: *BNIP1*, *C20orf24* (GenBank 55969), *CAT* (GenBank 847), *CD59* (GenBank 966), *ELL* (GenBank 8178), *GPX3* (GenBank 2878), *HTRA2* (GenBank 27429), *MOBP*, *MAPT*, *NFASC* (GenBank 114), *NSF*, *SCN5A* (GenBank 6331), *TEK* (GenBank 7010), *TNFAIP1* (GenBank 7126), and *TNIP1* (GenBank 10318). We found that *BNIP1* was significantly lower in motor neurons isolated from patients with ALS compared with controls (**Figure 2**A; eTable 6 in the Supplement). *MAPT* and *MOBP* were not differentially expressed in the motor neurons in patients with ALS and controls (eTable 6 in the Supplement).

Given the genetic overlap, we next examined *BNIP1* expression in the brains of patients with FTD and PSP. Compared with controls, the *BNIP1* expression was significantly reduced in the brains of patients with a neuropathologic diagnosis of FTD and PSP (Figure 2B and C). *MAPT* expression was not significantly altered in the brains of patients with FTD or PSP relative to controls (eTable 6 in the Supplement).

To further assess whether *BNIP1* expression is associated with ALS pathologic characteristics, we examined *BNIP1* expression in the spinal cords from a transgenic mouse model of ALS.[26,27] *BNIP1* expression was significantly reduced in the spinal cord of SOD1 G93A mice compared with SOD1 WT mice (Figure 2G). Thus, *BNIP1* expression is associated with ALS pathologic characteristics.

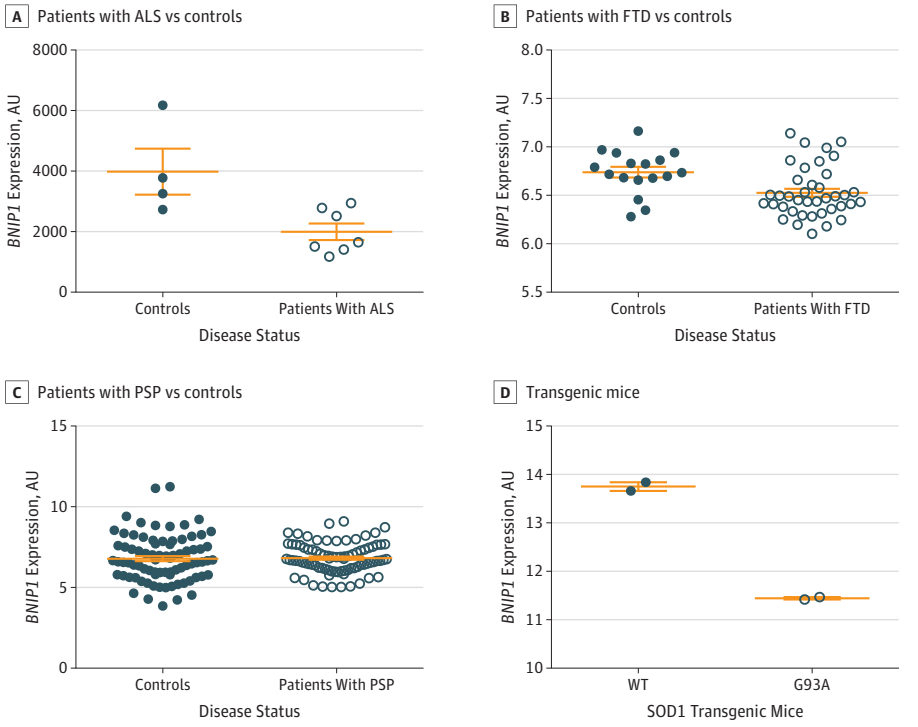
Table 3. Gene-Based Analysis of Shared Risk Genes[a]

GOID	GO Term	FDR
GO:0017075	Syntaxin-1 binding	2.59×10^{-6}
GO:0000149	SNARE binding	2.78×10^{-4}
GO:0048278	Vesicle docking	3.35×10^{-4}
GO:0034706	Sodium channel complex	1.46×10^{-3}
GO:0051648	Vesicle localization	2.17×10^{-3}
GO:0043209	Myelin sheath	2.28×10^{-3}
GO:0006887	Exocytosis	3.22×10^{-3}
GO:0016050	Vesicle organization	3.22×10^{-3}
GO:0051046	Regulation of secretion	3.90×10^{-3}
GO:0001518	Voltage-gated sodium channel complex	4.07×10^{-3}
GO:0015629	Actin cytoskeleton	5.45×10^{-3}
GO:0014854	Response to inactivity	5.65×10^{-3}
GO:0016684	Oxidoreductase activity	6.76×10^{-3}
GO:0019226	Transmission of nerve impulse	9.05×10^{-3}
GO:0051656	Establishment of organelle localization	0.01
GO:0051640	Organelle localization	0.01
GO:0004601	Peroxidase activity	0.01
GO:0043169	Cation binding	0.01
GO:0043198	Dendritic shaft	0.01
GO:1903561	Extracellular vesicle	0.02
GO:0005911	Cell-cell junction	0.02
GO:0030055	Cell-substrate junction	0.02
GO:0042744	Hydrogen peroxide catabolic process	0.02
GO:0043005	Neuron projection	0.02
GO:0046872	Metal ion binding	0.02
GO:0050678	Regulation of epithelial cell proliferation	0.03
GO:0048705	Skeletal system morphogenesis	0.03
GO:0070161	Anchoring junction	0.03
GO:0005925	Focal adhesion	0.03
GO:0051174	Regulation of phosphorus metabolic process	0.03
GO:0042743	Hydrogen peroxide metabolic process	0.04
GO:0086010	Membrane depolarization during action potential	0.04
GO:0019228	Neuronal action potential	0.04
GO:0030424	Axon	0.05

Abbreviations: FDR, false discovery rate; GO, Gene Ontology; GOID, Gene Ontology Identifier; SNARE, soluble *N*-ethylmaleimide sensitive fusion attachment protein receptor.

[a] Shared risk genes include genes nearest the single-nucleotide polymorphism and genes producing a *cis*-expression quantitative trait loci with the single-nucleotide polymorphism in conjunction and conditional FDR analyses.

Figure 2. Reduced *BNIP1* Expression in Neurodegenerative Tissue



A, Differential expression in motor neurons isolated from patients with amyotrophic lateral sclerosis (ALS) (GSE833 [Gene Expression Omnibus accession number]; mean [SEM] value, 3984 [760.8] arbitrary units [AU] for 4 controls and 1999 [274.1] AU for 7 patients with ALS; $P = .02$). B, Differential expression in homogenates from brains of patients with frontotemporal dementia (FTD) (GSE13162; mean [SEM] value, 6.7 [0.05] AU for 11 controls and 6.5 [0.04] AU for 17 patients with FTD; $P = .005$). C, Differential expression in homogenates from brains of patients with progressive supranuclear palsy (PSP) (syn6090802; mean [SEM] value, 6.8 [0.2] AU for 80 controls and 6.8 [0.1] AU for 84 patients with PSP; $P = .009$). D, Differential expression in homogenates from spinal cords of *SOD1* WT and *SOD1* G93A transgenic mice (GSE4390; mean [SEM] value, 13.8 [0.09] AU for 2 SOD1 WT mice and 11.5 [0.025] AU for 2 SOD1 G93A mice; $P = .002$).

Discussion

Using summary statistics from large GWASs (124 876 individuals) and established genetic methods, we investigated the genetic overlap between ALS, FTD (sporadic FTD and FTD with TDP-43 inclusions), PD, AD, CBD, and PSP. At a conjunction FDR of $P < .05$, we identified up to 300-fold enrichment in genetic risk for ALS across different levels of significance for FTD and PSP. Conjunction FDR analyses revealed shared loci previously associated with ALS risk as well as several loci not previously implicated in disease risk but that point to genetic drivers of neuronal function and mitophagy. Using this approach, we report novel genetic overlap between ALS and diseases of the FTD spectrum within the *MAPT* H1 haplotype.

We observed multiple signals within chromosome 9 that were associated with risk between ALS and FTD (the cohort defined by TDP-43 pathologic characteristics) and ALS and PSP. Among these, rs3849942 is associated with *C9orf72* repeat expansions that cause ALS and is used as a surrogate marker for the *C9orf72* expansion haplotype.[34-36] Consistent with these reports, our sQTL findings suggest that SNPs in LD with rs3849942 modify *C9orf72* splicing. Thus, it is likely that *C9orf72* expansion carriers are present in multiple data sets and are driving some of the association. However, given that rs3849942 is not in LD with a second SNP near *C9orf72*, 302855, we may be detecting an independent signal on chromosome 9 that is associated with the risk for ALS, FTD, and PSP.

Mutations in *MAPT* cause autosomal dominant forms of FTD.[37] Among FTD, PSP, and CBD, common variants in *MAPT* that tag the H1 haplotype represent the strongest genetic predictor of disease.[10,11,13,16-18] In addition, the *MAPT* H1 haplotype has been associated with PD and AD.[10,11,13,16-18] The *MAPT* H1 haplotype has recently been implicated in ALS risk in a meta-analysis of publications on neurodegenerative disease.[38] The risk SNP tagging the *MAPT* H1 haplotype, rs7224296, is associated with altered splicing of *MAPT* of exon 3, which, together with exon 2, encodes 2N-containing transcripts. Although the role that individual *MAPT* transcripts play in normal physiology and disease remains poorly understood, a recent study of human-induced pluripotent stem cell–derived neurons from *MAPT* haplotype carriers suggests that the H1 haplotype influences axonal transport velocities.[39] In ALS, these potential gene-induced deficits in axonal transport could alter disease onset and/or progression.

Conditional FDR analyses offer the opportunity to begin to reveal novel ALS risk loci. Using this approach, we identified 29 SNPs at a conditional FDR of $P < .05$. Within chromosome 5, we identified a risk locus at rs538622 (nearest gene, *ERGIC1*) that produced a significant eQTL in human brains with *BNIP1*. BNIP1 is a proapoptotic protein (Bcl-2 family member) involved in the regulation of endoplasmic reticulum structure and mitophagy.[40,41] *BNIP1* is highly expressed in neurons (eFigure 3 in the Supplement). More important, we demonstrate that *BNIP1* is significantly lower in central nervous system tissues from patients with ALS, FTD, and PSP. Because neuronal cell loss is a hallmark feature of neurodegenerative disease and because *BNIP1* is a neuronally expressed gene, we find that *BNIP1* is specifically reduced in both motor neurons isolated from the spinal cords of patients with ALS compared with the motor neu-

rons from matched controls. BNIP1 plays a critical role in mitophagy, a homeostatic mechanism for the selective degradation of damaged mitochondria.[42] Depletion of *BNIP1* in a cell model results in the disintegration of the endoplasmic reticulum network.[41] Given that endoplasmic reticulum stress and mitochondrial dysfunction have been implicated in ALS at the genetic, molecular, and cellular levels,[43] *BNIP1* may represent an important driver of pathologic characteristics.[44-46] Altered endoplasmic reticulum stress and mitochondrial dysfunction have been implicated in PSP and FTD.[47-52] The *MAPT* H1 haplotype has been shown to alter the axonal transport velocities of mitochondria, providing a biological connection to 2 of our most interesting genetic signals.[39]

Functionally, beyond mitophagy, we observed enrichment in shared risk genes occurring in pathways involved in neuronal health and maintenance. This finding, taken together with the relative lack of enrichment of genes in ALS, AD, and PD, points to the important role that genes involved in neuronal heath and function play in driving ALS, FTD, and PSP. Together, this study provides genetic, molecular, and functional insights into the effects of risk variants shared across the ALS-FTD spectrum.

Limitations

Beyond *BNIP1*, by leveraging statistical power from large neurodegenerative GWASs, we identified numerous novel ALS genetic variants. Although these SNPs warrant replication in an independent cohort, our findings suggest that sporadic ALS may represent a polygenic disorder characterized by numerous genetic variants, each of which has a small association with disease risk. Although no single common variant may be informative clinically, the additive combination of risk variants may help identify individuals who are at greatest genetic risk for ALS. The GWASs used in these analyses were performed for participants of European decent; thus, our findings of the genetic architecture of ALS and FTD spectrum disorders may be biased for individuals of European decent. Future studies conducted in large non-European populations will be critical for gaining a more complete understanding of the genetic architecture underlying ALS and FTD spectrum disorders.

Conclusions

By integrating GWAS data with gene expression data from neurodegenerative disease and transgenic mouse models, our multimodal findings implicate the *MAPT* H1 haplotype in ALS and *BNIP1* in the ALS-FTD spectrum. Additional work will be required to understand the role that tau plays in ALS and the relationship between *BNIP1*, mitophagy, and neurodegenerative diseases.

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