

UC San Diego

UC San Diego Previously Published Works

Title

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

Permalink

<https://escholarship.org/uc/item/01r1k8tv>

Journal

JAMA neurology, 75(7)

ISSN

2168-6149

Authors

Karch, Celeste M
Wen, Natalie
Fan, Chun C
[et al.](#)

Publication Date

2018-07-01

DOI

10.1001/jamaneurol.2018.0372

Peer reviewed

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

Celeste M. Karch, PhD; Natalie Wen; Chun C. Fan, MD; Jennifer S. Yokoyama, PhD; Naomi Kouri, PhD; Owen A. Ross, PhD; Gunter Höglinger, MD; Ulrich Müller, MD; Raffaele Ferrari, PhD; John Hardy, PhD; Gerard D. Schellenberg, PhD; Patrick M. Sleiman, PhD; Parastoo Momeni, PhD; Christopher P. Hess, MD, PhD; Bruce L. Miller, MD; Manu Sharma, PhD; Vivianna Van Deerlin, MD, PhD; Olav B. Smeland, MD, PhD; Ole A. Andreassen, MD, PhD; Anders M. Dale, PhD; Rahul S. Desikan, MD, PhD; for the International Frontotemporal Dementia (FTD)-Genomics Consortium, International Collaboration for Frontotemporal Dementia, Progressive Supranuclear Palsy (PSP) Genetics Consortium, and International Parkinson's Disease Genomics Consortium

Supplemental content

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.

JAMA Neurol. doi:10.1001/jamaneurol.2018.0372
Published online April 9, 2018.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the International Frontotemporal Dementia (FTD)-Genomics Consortium, International Collaboration for Frontotemporal Dementia, Progressive Supranuclear Palsy (PSP) Genetics Consortium, and International Parkinson's Disease Genomics Consortium are listed at the end of this article.

Corresponding Author: Celeste M. Karch, PhD, Department of Psychiatry, Washington University in St Louis, 425 S Euclid Ave, Campus Box 8134, St Louis, MO 63110 (karchc@wustl.edu).

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.

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

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.

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.

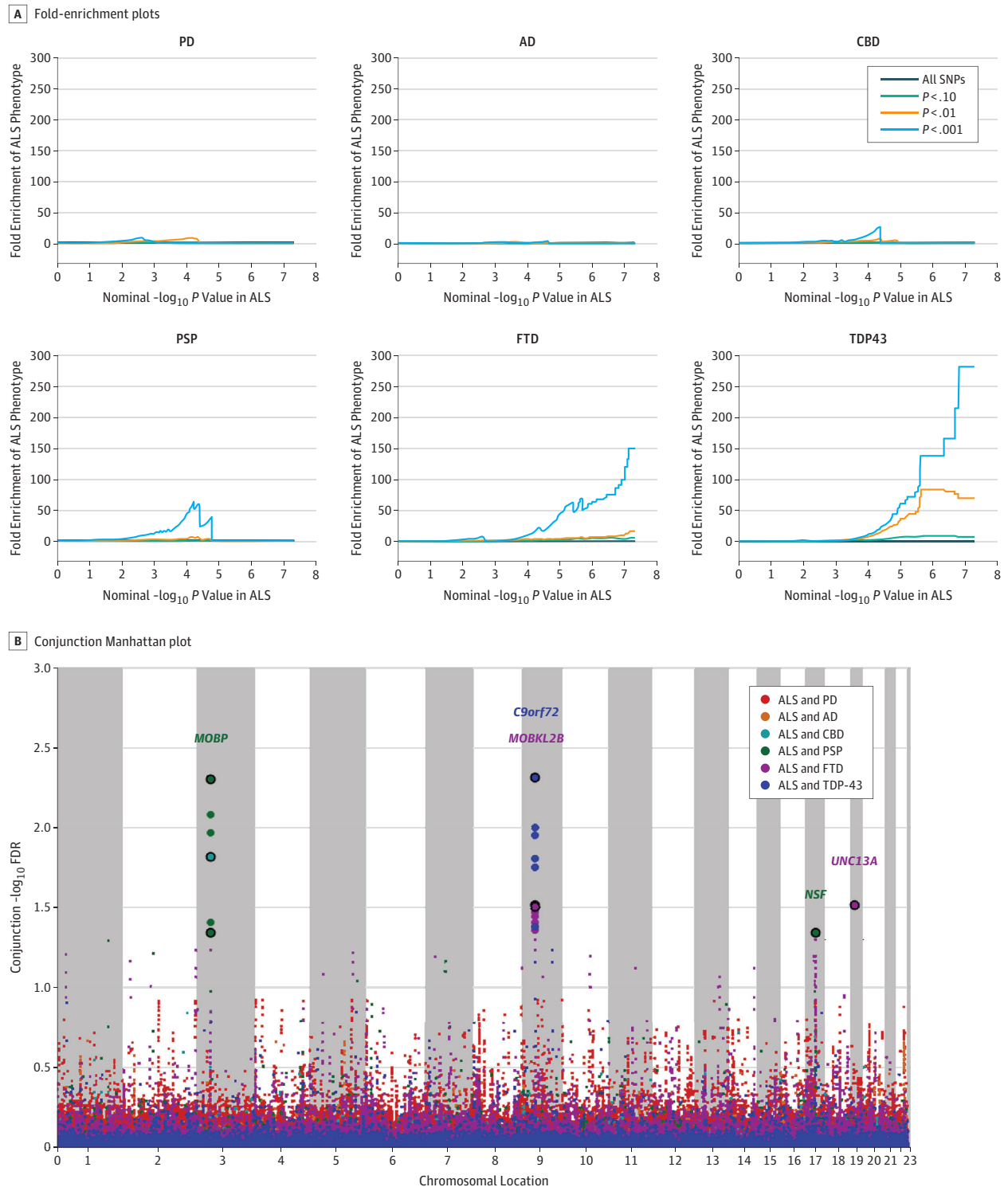
Results

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 PSP, 75-fold enrichment using FTD, 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)

SNP	Chr	Nearest Gene	eQTL	
			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}	MOBKLB
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, BCO45738 [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, 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 BNIPI (GenBank 662) such that the minor allele (G) is associated with the lower expression of BNIPI 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 Project³³ 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 post-synaptic 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 2A; 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. Com-

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

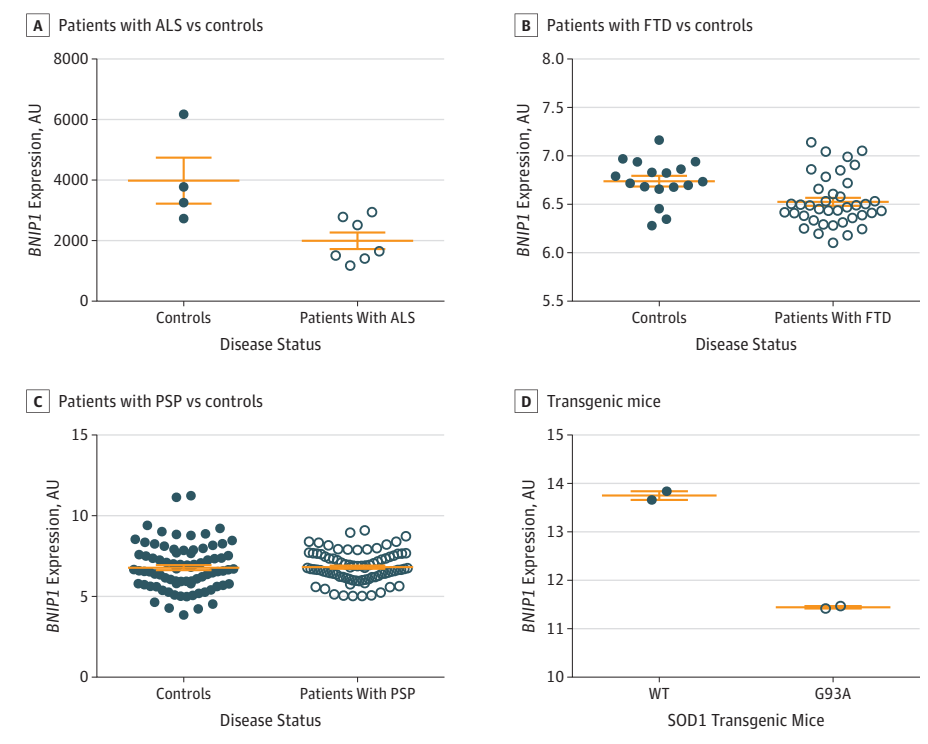
Abbreviations: FDR, false discovery rate; GO, Gene Ontology; GOID, Gene Ontology Identifier; SNARE, soluble *N*-ethylmaleimide sensitive fusion attachment protein receptor.

^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.

pared 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.

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 health 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 descent; thus, our findings of the genetic architecture of ALS and FTD spectrum disorders may be biased for individuals of European descent. 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.

ARTICLE INFORMATION

Accepted for Publication: January 12, 2018.

Published Online: April 9, 2018.

doi:10.1001/jamaneurol.2018.0372

Author Affiliations: Department of Psychiatry, Washington University in St Louis, St Louis, Missouri (Karch, Wen); Department of Cognitive Sciences, University of California, San Diego, La Jolla (Fan, Dale); Memory and Aging Center, Department of Neurodegeneration, German Center for Neurodegenerative Diseases, Munich, Germany (Höglinger); Department of Neurology, Technical University of Munich, Munich Cluster for Systems Neurology SyNergy, Munich, Germany (Höglinger); Institut für Humangenetik, Justus-Liebig-Universität, Giessen, Germany (Müller); Department of Molecular Neuroscience, Institute of Neurology, University College London, London, United Kingdom (Ferrari, Hardy); Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia (Schellenberg, Van Deerlin); Center for Applied Genomics, Abramson Research Center, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Sleiman); Division of Human Genetics, Abramson Research Center, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Sleiman); Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Sleiman); Laboratory of Neurogenetics, Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock

(Momeni); Neuroradiology Section, Department of Radiology and Biomedical Imaging, University of California, San Francisco (Hess, Desikan); Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany (Sharma); Institute for Clinical Epidemiology and Applied Biometry, University of Tübingen, Tübingen, Germany (Sharma); Norwegian Centre for Mental Disorders Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway (Smeland, Andreassen); Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway (Smeland, Andreassen); Department of Neurosciences, University of California, San Diego, La Jolla (Andreassen); Department of Neurosciences and Radiology, University of California, San Diego, La Jolla (Dale).

Author Contributions: Drs Karch and Desikan had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Karch, Hardy, Momeni, Miller, Andreassen, Dale, Desikan.

Acquisition, analysis, or interpretation of data: Karch, Wen, Fan, Yokoyama, Kouri, Ross, Höglinger, Müller, Ferrari, Schellenberg, Sleiman, Hess, Sharma, Van Deerlin, Smeland, Andreassen, Dale, Desikan.

Drafting of the manuscript: Karch, Wen, Momeni, Desikan.

Critical revision of the manuscript for important intellectual content: Karch, Fan, Yokoyama, Kouri, Ross, Höglinger, Müller, Ferrari, Hardy, Schellenberg, Sleiman, Hess, Miller, Sharma, Van Deerlin, Smeland, Andreassen, Dale.

Statistical analysis: Karch, Wen, Fan, Sleiman, Desikan.

Obtained funding: Karch, Ross, Höglinger, Schellenberg, Hess, Sharma, Desikan.

Administrative, technical, or material support: Kouri, Ross, Höglinger, Ferrari, Schellenberg, Sharma, Van Deerlin, Andreassen, Dale, Desikan.

Study supervision: Karch, Höglinger, Schellenberg, Andreassen, Desikan.

Conflict of Interest Disclosures: Dr Andreassen reported having a patent pending entitled *Systems and Methods for Identifying Polymorphisms*. No other disclosures were reported.

Funding/Support: This research was supported by grants NIH-AGO46374 (Dr Karch), KO1 AG049152 (Dr Yokoyama), and US4 NS100693 (Dr Ross) from the National Institutes of Health; grant 2016-A-005-SUP from the Larry J. Hillblom Foundation (Dr Yokoyama); a grant from KG Jebsen Stiftelsen (Dr Ross); grants 225989, 249711, and 223273 from the Research Council of Norway (Dr Andreassen); grant 2016-064 from the South East Norway Health Authority; a grant from the Norwegian Health Association; the American Society of Neuroradiology Foundation AD Imaging Award (Dr Desikan); the National Alzheimer's Coordinating Center Junior Investigator Award (Dr Desikan); grant 282 from the Alzheimer's Society (Dr Ferrari); grants from the Tau Consortium (Drs Karch and Yokoyama); and grants from the Deutsche Forschungsgemeinschaft (DFG, HO2402/6-2 & Munich Cluster for Systems Neurology SyNergy), the German Federal Ministry of Education and Research (BMBF, O1KU1403A EpiPD; O1EK1605A HitTau), and the NOMIS Foundation (FTLD project) (Dr Höglinger).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and

interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: *The Progressive Supranuclear Palsy (PSP) Genetics Consortium* members include Günter U. Höglinger, Department of Neurology, Philipps-Universität, Marburg, Germany; Nadine M. Melhem, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Dennis W. Dickson, Department of Neuroscience, Mayo Clinic, Jacksonville, Florida; Patrick M. A. Sleiman, Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Li-San Wang, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia; Lambertus Klei, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Rosa Rademakers, Department of Neuroscience, Mayo Clinic, Jacksonville, Florida; Rohan de Silva, Reta Lila Weston Institute, University College London Institute of Neurology, London, UK; Irene Litvan, Department of Neurology, Division of Movement Disorders, University of Louisville, Louisville, Kentucky; David E. Riley, Department of Neurology, University Hospitals, Case Western Reserve University, Cleveland, Ohio; John C. van Swieten, Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands; Peter Heutink, Department of Clinical Genetics, Vrije Universiteit Medical Center, Section Medical Genomics, Amsterdam, the Netherlands; Zbigniew K. Wszolek, Department of Neurology, Mayo Clinic, Jacksonville, Florida; Ryan J. Uitti, Department of Neurology, Mayo Clinic, Jacksonville, Florida; Jana Vandrovцова, Reta Lila Weston Institute, University College London Institute of Neurology, London, UK; Howard I. Hurtig, Department of Neurology, University of Pennsylvania Health System, Philadelphia; Rachel G. Gross, Department of Neurology, University of Pennsylvania Health System, Philadelphia; Walter Maetzler, Center of Neurology, Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, and German Center for Neurodegenerative Diseases, University of Tübingen, Tübingen, Germany; Stefano Goldwurm, Parkinson Institute, Istituti Clinici di Perfezionamento, Milano, Italy; Eduardo Tolosa, Neurology Service, Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain; Barbara Borroni, Department of Medical and Surgical Sciences, Institute of Neurology, University of Brescia, Brescia, Italy; Pau Pastor, Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Instituto de Salud Carlos III, Madrid, Spain, Department of Neurology, University of Navarra, Clínica Universidad de Navarra, Pamplona, Spain; PSP Genetics Study Group; Laura B. Cantwell, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Mi Ryung Han, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Allissa Dillman, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Marcel P. van der Brug, Department of Neuroscience, The Scripps Research Institute, Jupiter, Florida; J. Raphael Gibbs, Reta Lila

Weston Institute, University College London Institute of Neurology, London, UK, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Mark R. Cookson, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Dena G. Hernandez, Reta Lila Weston Institute, University College London Institute of Neurology, London, UK, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Andrew B. Singleton, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Matthew J. Farrer, Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada; Chang-En Yu, Department of Medicine, University of Washington School of Medicine, Seattle, Washington, Geriatric Research, Education, and Clinical Center (GRECC), Veterans Affairs Puget Sound Health Care System, Seattle, Washington; Lawrence I. Golbe, Department of Neurology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, New Jersey; Tamas Revesz, Department of Molecular Neuroscience, Queen Square Brain Bank for Neurological Disorders, University College London Institute of Neurology, University College London, London, UK; John Hardy, Reta Lila Weston Institute, University College London Institute of Neurology, London, UK; Andrew J Lees, Reta Lila Weston Institute, University College London Institute of Neurology, London, UK, Department of Molecular Neuroscience, Queen Square Brain Bank for Neurological Disorders, University College London Institute of Neurology, University College London, London, UK; Bernie Devlin, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Hakon Hakonarson, Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Ulrich Müller, Institut für Humangenetik, Justus-Liebig-Universität, Giessen, Germany; Gerard D. Schellenberg, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Roger L. Albin, Department of Neurology, University of Michigan, Ann Arbor, Michigan, Geriatrics Research, Education, and Clinical Center, Veterans Affairs Ann Arbor Health System, Ann Arbor, Michigan; Elena Alonso, Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Instituto de Salud Carlos III, Madrid, Spain, Neurogenetics Laboratory, Division of Neurosciences, University of Navarra Center for Applied Medical Research, Pamplona, Spain; Angelo Antonini, Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy, Department for Parkinson's Disease, Istituto Di Ricovero e Cura a Carattere Scientifico San Camillo, Venice, Italy; Manuela Apfelbacher, Institute of Legal Medicine, University of Würzburg, Würzburg, Germany; Steven E. Arnold, Department of Psychiatry, Center for Neurobiology and Behavior, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Jesus Avila, Centro de Biología Molecular Severo Ochoa (CSIC-UAM), Campus Cantoblanco, Universidad Autónoma de Madrid, Madrid, Spain; Thomas G. Beach, Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, Arizona; Sherry Beecher, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Daniela Berg, Center of

Neurology, Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen and German Center for Neurodegenerative Diseases, Tübingen, Germany; Thomas D. Bird, Geriatrics Research Education and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, Washington; Nenad Bogdanovic, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Hudding University Hospital, Stockholm, Sweden; Agnita J. W. Boon, Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands; Yvette Bordelon, Department of Neurology, University of California Los Angeles; Alexis Brice, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Université Pierre et Marie Curie, Institut National de la Santé et de la Recherche Médicale, and Centre National de la Recherche Scientifique, Paris, France; Herbert Budka, Institute of Neurology, Medical University Vienna, Vienna, Austria; Margherita Canesi, Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy; Wang Zheng Chiu, Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands; Roberto Cilia, Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy; Carlo Colosimo, Dipartimento di Scienze Neurologiche e Psichiatriche, Sapienza Università di Roma, Rome, Italy; Peter P. De Deyn, Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium; Justo García de Yébenes, Department of Neurology, Hospital Ramón y Cajal, Madrid, Spain; Laura Donker Kaat, Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands; Ranjan Duara, Wien Center for Alzheimer's Disease and Memory Disorders, Mt. Sinai Medical Center, Miami Beach, Florida; Alexandra Durr, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Université Pierre et Marie Curie, Institut National de la Santé et de la Recherche Médicale, and Centre National de la Recherche Scientifique, Paris, France; Sebastiaan Engelborghs, Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium; Giovanni Fabbri, Dipartimento di Scienze Neurologiche e Psichiatriche, Sapienza Università di Roma, Rome, Italy; Nicole A. Finch, Department of Neuroscience, Mayo Clinic, Jacksonville, Florida; Robyn Flook, Centre for Neuroscience, Flinders University and Australian Brain Bank Network, Victoria, Australia; Matthew P. Frosch, C. S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital and Harvard Medical School, Boston; Carles Gaig, Neurology Service, Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Hospital Clínic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain; Douglas R. Galasko, Department of Neurosciences, University of California San Diego, La Jolla; Thomas Gasser, Center of Neurology, Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen and German Center for Neurodegenerative Diseases, Tübingen, Germany; Marla Gearing, Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia; Evan T. Geller, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia; Bernardino Ghetti, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis; Neill R. Graff-Radford, Department of Neurology, Mayo Clinic, Jacksonville, Florida; Murray Grossman, Department of Neurology, University of

Pennsylvania Health System, Philadelphia; Deborah A. Hall, Department of Neurological Sciences, Rush University, Chicago, Illinois; Lili-Naz Hazrati, Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada; Matthias Höllerherge, Department of Neurology, Philipps University, Marburg, Germany; Joseph Jankovic, Department of Neurology, Baylor College of Medicine, Houston, Texas; Jorge L. Juncos, Department of Neurology, Emory University, Atlanta, Georgia; Anna Karydas, Department of Neurology, Memory and Aging Center, University of California, San Francisco; Hans A. Kretschmar, Institut für Neuropathologie, Ludwig-Maximilians-Universität and Brain Net Germany, Munich, Germany; Isabelle Leber, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Université Pierre et Marie Curie, Institut National de la Santé et de la Recherche Médicale, and Centre National de la Recherche Scientifique, Paris, France; Virginia M. Lee, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia; Andrew P. Lieberman, Department of Pathology, University of Michigan Medical School, Ann Arbor; Kelly E. Lyons, Department of Neurology, University of Kansas Medical Center, Kansas City; Claudio Mariani, Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy; Eliezer Masliah, Department of Neurosciences, University of California San Diego, La Jolla, and Department of Pathology, University of California San Diego, La Jolla; Luke A. Massey, Reta Lila Weston Institute, University College London Institute of Neurology, University College London, London, UK; Catriona A. McLean, Victorian Brain Bank Network, Mental Health Research Institute, Victoria, Australia; Nicoletta Meucci, Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy; Bruce L. Miller, Department of Neurology, Memory and Aging Center, University of California, San Francisco; Brit Mollenhauer, Department of Neurology, Georg-August University, Goettingen, Germany, and Paracelsus-Elena-Klinik, University of Goettingen, Kassel, Germany; Jens C. Möller, Department of Neurology, Philipps University, Marburg, Germany; Huw R. Morris, Medical Research Council Centre for Neuropsychiatric Genetics and Department of Neurology, School of Medicine, Cardiff University, Cardiff, UK; Chris Morris, Newcastle Brain Tissue Resource, Newcastle University, Institute for Ageing and Health, Newcastle upon Tyne, UK; Sean S. O'Sullivan, Reta Lila Weston Institute, University College London Institute of Neurology, University College London, London, UK; Wolfgang H. Oertel, Department of Neurology, Philipps University, Marburg, Germany; Donatella Ottaviani, Dipartimento di Scienze Neurologiche e Psichiatriche, Sapienza Università di Roma, Rome, Italy; Alessandro Padovani, Department of Medical and Surgical Sciences, Institute of Neurology, University of Brescia, Brescia, Italy; Rajesh Pahwa, Department of Neurology, University of Kansas Medical Center, Kansas City; Gianni Pezzoli, Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy; Stuart Pickering-Brown, Neurodegeneration and Mental Health Research Group, Faculty of Human and Medical Sciences, University of Manchester, Manchester, UK; Werner Poewe, Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; Alberto Rabano, Department of Neuropathology and Tissue Bank, Fundación Centro Investigación Enfermedades Neurológicas, Instituto de Salud Carlos III, Madrid,

Spain; Alex Rajput, Division of Neurology, Royal University Hospital, University of Saskatchewan, Saskatchewan, Canada; Stephen G. Reich, Department of Neurology, University of Maryland School of Medicine, Baltimore; Gesine Respondek, Department of Neurology, Philipps University, Marburg, Germany; Sigrun Roeber, Institut für Neuropathologie, Ludwig-Maximilians-Universität and Brain Net Germany, Munich, Germany; Jonathan D. Rohrer, Department of Neurodegenerative Disease, Dementia Research Centre, University College London Institute of Neurology, University College London, London, UK; Owen A. Ross, Department of Neuroscience, Mayo Clinic, Jacksonville, Florida; Martin N. Rossor, Department of Neurodegenerative Disease, Dementia Research Centre, University College London Institute of Neurology, University College London, London, UK; Giorgio Sacilotto, Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy; William W. Seeley, Department of Neurology, Memory and Aging Center, University of California, San Francisco; Klaus Seppi, Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; Laura Silveira-Moriyama, Reta Lila Weston Institute, University College London Institute of Neurology, University College London, London, UK; Salvatore Spina, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis; Karin Srulijes, Center of Neurology, Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen and German Center for Neurodegenerative Diseases, Tübingen, Germany; Peter St George-Hyslop, Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada, and Cambridge Institute for Medical Research and Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK; Maria Stamelou, Department of Neurology, Philipps University, Marburg, Germany; David G. Standaert, Department of Neurology, Center for Neurodegeneration and Experimental Therapeutics, University of Alabama at Birmingham; Silvana Tesei, Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy; Wallace W. Tourtellotte, Human Brain and Spinal Fluid Resource Center, Veterans Affairs West Los Angeles Healthcare Center, Los Angeles, California; Claudia Trenkwalder, Paracelsus-Elena-Klinik, University of Goettingen, Kassel, Germany; Claire Troakes, Department of Clinical Neuroscience, Medical Research Council Centre for Neurodegeneration Research, King's College London, London, UK; John Q. Trojanowski, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia; Juan C. Troncoso, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland; Vivianna M. Van Deerlin, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia; Jean Paul G. Vonsattel, Department of Pathology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, New York; Gregor K. Wenning, Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; Charles L. White, Department of Pathology, University of Texas Southwestern Medical Center, Dallas; Pia Winter, Institute of Human Genetics, Justus-Liebig University, Giessen, Germany; Chris Zarow, Rancho Los Amigos National Rehabilitation Center, University of Southern California, Downey;

and Anna L. Zecchinelli, Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy.

The International Frontotemporal Dementia (FTD)-Genomics Consortium members include Raffaele Ferrari, Department of Molecular Neuroscience, University College London, London, UK; Dena G. Hernandez, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, and Reta Lila Weston Research Laboratories, Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; Michael A. Nalls, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Jonathan D. Rohrer, Reta Lila Weston Research Laboratories, Department of Molecular Neuroscience, University College London Institute of Neurology, and Dementia Research Centre, Department of Neurodegenerative Disease, University College London Institute of Neurology, London, UK; Adaikalavan Ramasamy, Reta Lila Weston Research Laboratories, Department of Molecular Neuroscience, University College London Institute of Neurology, and Department of Medical and Molecular Genetics, King's College London Tower Wing, Guy's Hospital, London, UK, and The Jenner Institute, University of Oxford, Oxford, UK; John B. J. Kwok, Neuroscience Research Australia, and School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia; Carol Dobson-Stone, Neuroscience Research Australia, and School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia; William S. Brooks, Neuroscience Research Australia, and Prince of Wales Clinical School, University of New South Wales, Sydney, New South Wales, Australia; Peter R. Schofield, Neuroscience Research Australia, and School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia; Glenda M. Halliday, Neuroscience Research Australia, and School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia; John R. Hodges, Neuroscience Research Australia, and School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia; Olivier Piguet, Neuroscience Research Australia, and School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia; Lauren Bartley, Neuroscience Research Australia, Sydney, New South Wales, Australia; Elizabeth Thompson, South Australian Clinical Genetics Service, South Australian Pathology, Women's and Children's Hospital, North Adelaide, South Australia, Australia, and Department of Paediatrics, University of Adelaide, Adelaide, South Australia, Australia; Eric Haan, South Australian Clinical Genetics Service, South Australian Pathology, Women's and Children's Hospital, North Adelaide, South Australia, Australia, and Department of Paediatrics, University of Adelaide, Adelaide, South Australia, Australia; Isabel Hernández, Research Center and Memory Clinic of Fundació Alzheimer's Education Center, Institut Català de Neurociències Aplicades, Barcelona, Spain; Agustín Ruiz, Research Center and Memory Clinic of Fundació Alzheimer's Education Center, Institut Català de Neurociències Aplicades, Barcelona, Spain; Mercè Boada, Research Center and Memory Clinic of Fundació Alzheimer's Education Center, Institut Català de Neurociències Aplicades, Barcelona, Spain; Barbara Borroni, Neurology Clinic, University of Brescia,

Brescia, Italy; Alessandro Padovani, Neurology Clinic, University of Brescia, Brescia, Italy; Carlos Cruchaga, Department of Psychiatry, Washington University in St Louis, and Hope Center, Washington University School of Medicine, St Louis, Missouri; Nigel J. Cairns, Hope Center, Washington University School of Medicine, and Department of Pathology and Immunology, Washington University in St Louis, St Louis, Missouri; Luisa Benussi, Molecular Markers Laboratory, Istituto di Ricovero e Cura a Carattere Scientifico Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy; Giuliano Binetti, Memory and Aging Clinic Memory Clinic, Istituto di Ricovero e Cura a Carattere Scientifico Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy; Gianluigi Forloni, Biology of Neurodegenerative Disorders, Istituto di Ricovero e Cura a Carattere Scientifico Istituto di Ricerche Farmacologiche, "Mario Negri," Milano, Italy; Diego Albiani, Biology of Neurodegenerative Disorders, Istituto di Ricovero e Cura a Carattere Scientifico Istituto di Ricerche Farmacologiche "Mario Negri," Milano, Italy; Daniela Galimberti, University of Milan, and Fondazione Cà Granda, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Maggiore Policlinico, Milan, Italy; Chiara Fenoglio, University of Milan, and Fondazione Cà Granda, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Maggiore Policlinico, Milan, Italy; Elio Scarpini, University of Milan, and Fondazione Cà Granda, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Maggiore Policlinico, Milan, Italy; Jordi Clarimón, Memory Unit, Neurology Department and Sant Pau Biomedical Research Institute, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain, and Center for Networker Biomedical Research in Neurodegenerative Diseases (CIBERNED), Madrid, Spain; Alberto Leó, Memory Unit, Neurology Department and Sant Pau Biomedical Research Institute, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain, and Center for Networker Biomedical Research in Neurodegenerative Diseases (CIBERNED), Madrid, Spain; Rafael Blesa, Memory Unit, Neurology Department and Sant Pau Biomedical Research Institute, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain, and Center for Networker Biomedical Research in Neurodegenerative Diseases (CIBERNED), Madrid, Spain; Maria Landqvist Waldö, Unit of Geriatric Psychiatry, Department of Clinical Sciences, Lund University, Lund, Sweden; Karin Nilsson, Unit of Geriatric Psychiatry, Department of Clinical Sciences, Lund University, Lund, Sweden; Christer Nilsson, Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden; Ian RA Mackenzie, Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada; Ging-Yuek R. Hsiung, Division of Neurology, University of British Columbia, Vancouver, British Columbia, Canada; David M. A. Mann, Institute of Brain, Behaviour and Mental Health, University of Manchester, Salford Royal Hospital, Salford, UK;

Jordan Grafman, Rehabilitation Institute of Chicago, Departments of Physical Medicine and Rehabilitation, Psychiatry, and Cognitive Neurology & Alzheimer's Disease Center, Feinberg School of Medicine, Northwestern University, and Department of Psychology, Weinberg College of Arts and Sciences, Northwestern University, Chicago, Illinois; Christopher M. Morris, Newcastle Brain Tissue Resource, Institute for Ageing, Newcastle University, Newcastle University, Institute of Neuroscience and Institute for Ageing, Campus for Ageing and Vitality, and Institute of Neuroscience, Newcastle University Medical School, Newcastle upon Tyne, UK; Johannes Attems, Newcastle University, Institute of Neuroscience and Institute for Ageing, Campus for Ageing and Vitality, Newcastle upon Tyne, UK; Timothy D. Griffiths, Institute of Neuroscience, Newcastle University Medical School, Newcastle upon Tyne, UK; Ian G. McKeith, Newcastle University, Institute of Neuroscience and Institute for Ageing, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, UK; Alan J. Thomas, Newcastle University, Institute of Neuroscience and Institute for Ageing, Campus for Ageing and Vitality, Newcastle upon Tyne, UK; Pietro Pietrini, Institutions, Markets, Technologies School for Advanced Studies, Lucca, Italy; Edward D. Huey, Taub Institute, Departments of Psychiatry and Neurology, Columbia University, New York, New York; Eric M. Wassermann, Behavioral Neurology Unit, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland; Atik Baborie, Department of Laboratory Medicine & Pathology, Walter Mackenzie Health Sciences Centre, University of Alberta Edmonton, Edmonton, Alberta, Canada; Evelyn Jaros, Newcastle University, Institute for Ageing and Health, Campus for Ageing and Vitality, Newcastle upon Tyne, UK; Michael C. Tierney, Behavioral Neurology Unit, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland; Pau Pastor, Center for Networker Biomedical Research in Neurodegenerative Diseases (CIBERNED), Madrid, Spain, and Neurogenetics Laboratory, Division of Neurosciences, Center for Applied Medical Research, Universidad de Navarra, and Department of Neurology, Clínica Universidad de Navarra, University of Navarra School of Medicine, Pamplona, Spain; Cristina Razquin, Neurogenetics Laboratory, Division of Neurosciences, Center for Applied Medical Research, Universidad de Navarra, Pamplona, Spain; Sara Ortega-Cubero, Center for Networker Biomedical Research in Neurodegenerative Diseases (CIBERNED), Madrid, Spain, and Neurogenetics Laboratory, Division of Neurosciences, Center for Applied Medical Research, Universidad de Navarra, Pamplona, Spain; Elena Alonso, Neurogenetics Laboratory, Division of Neurosciences, Center for Applied Medical Research, Universidad de Navarra, Pamplona, Spain; Robert Perneczky, Neuroepidemiology and Ageing Research Unit, School of Public Health, Faculty of Medicine, The Imperial College of Science, Technology and Medicine, and West London Cognitive Disorders Treatment and Research Unit, West London Mental Health Trust, London, UK, and Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany; Janine Diehl-Schmid, Department of Psychiatry and Psychotherapy, Technische Universität München,

Munich, Germany; Panagiotis Alexopoulos, Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany; Alexander Kurz, Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany; Innocenzo Rainero, Neurology I, Department of Neuroscience, University of Torino, A. O. Città della Salute e della Scienza di Torino, Torino, Italy; Elisa Rubino, Neurology I, Department of Neuroscience, University of Torino, A. O. Città della Salute e della Scienza di Torino, Torino, Italy; Lorenzo Pinessi, Neurology I, Department of Neuroscience, University of Torino, A. O. Città della Salute e della Scienza di Torino, Torino, Italy; Ekaterina Rogava, Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada; Peter St George-Hyslop, Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada, and Cambridge Institute for Medical Research, and the Department of Clinical Neurosciences, University of Cambridge, Hills Road, Cambridge, UK; Giacomina Rossi, Division of Neurology V and Neuropathology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milano, Italy; Fabrizio Tagliavini, Division of Neurology V and Neuropathology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milano, Italy; James B. Rowe, Cambridge University Department of Clinical Neurosciences, Medical Research Council Cognition and Brain Sciences Unit, and Behavioural and Clinical Neuroscience Institute, Cambridge, UK; Johannes CM Schlachetzki, Department of Cellular & Molecular Medicine, University of California San Diego, La Jolla; James Uphill, Medical Research Council Prion Unit, Department of Neurodegenerative Disease, University College London Institute of Neurology, London, UK; John Collinge, Medical Research Council Prion Unit, Department of Neurodegenerative Disease, University College London Institute of Neurology, London, UK; Simon Mead, Medical Research Council Prion Unit, Department of Neurodegenerative Disease, University College London Institute of Neurology, London, UK; Adrian Danek, Neurologische Klinik und Poliklinik, Ludwig-Maximilians-Universität, and German Center for Neurodegenerative Diseases (DZNE), Munich, Germany; Vivianna M. Van Deerlin, Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia; Murray Grossman, Department of Neurology and Penn Frontotemporal Degeneration Center, University of Pennsylvania Perelman School of Medicine, Philadelphia; John Q. Trojanowski, Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia; Julie van der Zee, Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, Vlaams Instituut voor Biotechnologie, and Laboratory of Neurogenetics, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium; Marc Cruts, Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, Vlaams Instituut voor Biotechnologie, and Laboratory of Neurogenetics, Institute Born-Bunge, University of

Antwerp, Belgium; Christine Van Broeckhoven, Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, Vlaams Instituut voor Biotechnologie, and Laboratory of Neurogenetics, Institute Born-Bunge, University of Antwerp, Belgium; Stefano F. Cappa, Neurorehabilitation Unit, Department of Clinical Neuroscience, Vita-Salute University and San Raffaele Scientific Institute, Milan, Italy; Isabelle Leber, Inserm, UMR_S975, CRICM; UPMC University Paris 06, UMR_S975, CNRS UMR 7225, F-75013, and AP-HP, Hôpital de la Salpêtrière, Département de neurologie-centre de références des démences rares, Paris, France; Didier Hannequin, Service de Neurologie, Inserm U1079, CNR-MAJ, Rouen University Hospital, Rouen, France; Véronique Golfer, Service de neurologie, CH Saint Briec, France; Martine Vercelletto, Service de neurologie, CHU Nantes, France; Alexis Brice, Inserm, UMR_S975, CRICM; UPMC University Paris 06, UMR_S975, CNRS UMR 7225, F-75013, and AP-HP, Hôpital de la Salpêtrière, Département de neurologie-centre de références des démences rares, Paris, France; Benedetta Nacmias, Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy; Sandro Sorbi, Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, and Istituto di Ricovero e Cura a Carattere Scientifico "Don Carlo Gnocchi" Firenze, Florence, Italy; Silvia Bagnoli, Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy; Irene Piaceri, Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy; Jørgen E. Nielsen, Danish Dementia Research Centre, Neurogenetics Clinic, Department of Neurology, Rigshospitalet, Copenhagen University Hospital, and Department of Cellular and Molecular Medicine, Section of Neurogenetics, The Panum Institute, University of Copenhagen, Copenhagen, Denmark; Lena E. Hjermand, Danish Dementia Research Centre, Neurogenetics Clinic, Department of Neurology, Rigshospitalet, Copenhagen University Hospital, and Department of Cellular and Molecular Medicine, Section of Neurogenetics, The Panum Institute, University of Copenhagen, Copenhagen, Denmark; Matthias Riemenschneider, Saarland University Hospital, Department for Psychiatry & Psychotherapy, and Saarland University, Laboratory for Neurogenetics, Homburg/Saar, Germany; Manuel Mayhaus, Saarland University, Laboratory for Neurogenetics, Homburg/Saar, Germany; Bernd Ibach, University Regensburg, Department of Psychiatry, Psychotherapy and Psychosomatics, Regensburg, Germany; Gilles Gasparoni, Saarland University, Laboratory for Neurogenetics, Homburg/Saar, Germany; Sabrina Pichler, Saarland University, Laboratory for Neurogenetics, Homburg/Saar, Germany; Wei Gu, Saarland University, Laboratory for Neurogenetics, Homburg/Saar, Germany, and Luxembourg Centre For Systems Biomedicine (LCSB), University of Luxembourg 7, Esch-sur-Alzette, Luxembourg; Martin N. Rossor, Dementia Research Centre, Department of Neurodegenerative Disease, University College London Institute of Neurology, London, UK; Nick C. Fox, Dementia Research Centre, Department of Neurodegenerative Disease, University College London Institute of Neurology,

London, UK; Jason D. Warren, Dementia Research Centre, Department of Neurodegenerative Disease, University College London Institute of Neurology, London, UK; Maria Grazia Spillantini, University of Cambridge, Department of Clinical Neurosciences, John Van Geest Brain Repair Centre, Cambridge, UK; Huw R. Morris, University College London, Department of Molecular Neuroscience, London, UK; Patrizia Rizzu, German Center for Neurodegenerative Diseases-Tübingen, Tuebingen, Germany; Peter Heutink, German Center for Neurodegenerative Diseases-Tübingen, Tuebingen, Germany; Julie S. Snowden, Institute of Brain, Behaviour and Mental Health, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK; Sara Rollinson, Institute of Brain, Behaviour and Mental Health, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK; Anna Richardson, Salford Royal Foundation Trust, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK; Alexander Gerhard, Institute of Brain, Behaviour and Mental Health, The University of Manchester, Manchester, UK; Amalia C. Bruni, Regional Neurogenetic Centre, Azienda Sanitaria Provinciale Catanzaro, Lamezia Terme, Italy; Raffaele Maletta, Regional Neurogenetic Centre, Azienda Sanitaria Provinciale Catanzaro, Lamezia Terme, Italy; Francesca Frangipane, Regional Neurogenetic Centre, Azienda Sanitaria Provinciale Catanzaro, Lamezia Terme, Italy; Chiara Cupidi, Regional Neurogenetic Centre, Azienda Sanitaria Provinciale Catanzaro, Lamezia Terme, Italy; Livia Bernardi, Regional Neurogenetic Centre, Azienda Sanitaria Provinciale Catanzaro, Lamezia Terme, Italy; Maria Anfossi, Regional Neurogenetic Centre, Azienda Sanitaria Provinciale Catanzaro, Lamezia Terme, Italy; Maura Gallo, Regional Neurogenetic Centre, Azienda Sanitaria Provinciale Catanzaro, Lamezia Terme, Italy; Maria Elena Conidi, Regional Neurogenetic Centre, Azienda Sanitaria Provinciale Catanzaro, Lamezia Terme, Italy; Nicoletta Smirne, Regional Neurogenetic Centre, Azienda Sanitaria Provinciale Catanzaro, Lamezia Terme, Italy; Rosa Rademakers, Department of Neuroscience, Mayo Clinic Jacksonville, Jacksonville, Florida; Matt Baker, Department of Neuroscience, Mayo Clinic Jacksonville, Jacksonville, Florida; Dennis W. Dickson, Department of Neuroscience, Mayo Clinic Jacksonville, Jacksonville, Florida; Neill R. Graff-Radford, Department of Neurology, Mayo Clinic Jacksonville, Jacksonville, Florida; Ronald C. Petersen, Department of Neurology, Mayo Clinic Rochester, Rochester, Minnesota; David Knopman, Department of Neurology, Mayo Clinic Rochester, Rochester, Minnesota; Keith A. Josephs, Department of Neurology, Mayo Clinic Rochester, Rochester, Minnesota; Bradley F. Boeve, Department of Neurology, Mayo Clinic Rochester, Rochester, Minnesota; Joseph E. Parisi, Department of Pathology, Mayo Clinic Rochester, Rochester, Minnesota; William W. Seeley, Department of Neurology, University of California, San Francisco; Anna M. Karydas, Memory and Aging Center, Department of Neurology, University of California, San Francisco; Bruce L. Miller, Memory and Aging Center, Department of Neurology, University of California, San Francisco; Anna M. Karydas, Memory and Aging Center, Department of Neurology, University of California, San Francisco; Howard Rosen, Memory and Aging Center, Department of Neurology, University of California, San Francisco; John C. van Swieten, Department of Neurology, Erasmus Medical Centre, Rotterdam, the Netherlands, and Department of Medical Genetics, Vrije Universiteit

University Medical Centre, Amsterdam, the Netherlands; Elise G. P. Dopper, Department of Neurology, Erasmus Medical Centre, Rotterdam, the Netherlands; Harro Seelaar, Department of Neurology, Erasmus Medical Centre, Rotterdam, the Netherlands; Yolande A. L. Pijnenburg, Alzheimer Centre and Department of Neurology, Vrije Universiteit University Medical Centre, Amsterdam, the Netherlands; Philip Scheltens, Alzheimer Centre and Department of Neurology, Vrije Universiteit University Medical Centre, Amsterdam, the Netherlands; Giancarlo Logroscino, Department of Basic Medical Sciences, Neurosciences and Sense Organs of the "Aldo Moro" University of Bari, Bari, Italy; Rosa Capozzo, Department of Basic Medical Sciences, Neurosciences and Sense Organs of the "Aldo Moro" University of Bari, Bari, Italy; Valeria Novelli, Medical Genetics Unit, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; Annibale A. Puca, Cardiovascular Research Unit, Istituto di Ricovero e Cura a Carattere Scientifico Multimedica, Milan, Italy, and Department of Medicine and Surgery, University of Salerno, Baronissi, Italy; Massimo Franceschi, Neurology Department, Istituto di Ricovero e Cura a Carattere Scientifico Multimedica, Milan, Italy; Alfredo Postiglione, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy; Graziella Milan, Geriatric Center Frullone-Azienda Sanitaria Locale Napoli 1 Centro, Naples, Italy; Paolo Sorrentino, Geriatric Center Frullone-Azienda Sanitaria Locale Napoli 1 Centro, Naples, Italy; Mark Kristiansen, University College London Genomics, Institute of Child Health (ICH), University College London, London, UK; Huei-Hsin Chiang, Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Alzheimer Research Center, Novum, and Department of Geriatric Medicine, Genetics Unit, Karolinska University Hospital, Stockholm, Sweden; Caroline Graff, Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Alzheimer Research Center, Novum, Stockholm, and Department of Geriatric Medicine, Genetics Unit, Karolinska University Hospital, Stockholm, Sweden; Florence Pasquier, University Lille, Inserm 1171, DistAlz, CHU 59000, Lille, France; Adeline Rollin, University Lille, Inserm 1171, DistAlz, CHU 59000, Lille, France; Vincent Deramecourt, University Lille, Inserm 1171, DistAlz, CHU 59000, Lille, France; Thibaud Lebouvier, University Lille, Inserm 1171, DistAlz, CHU 59000, Lille, France; Dimitrios Kapogiannis, National Institute on Aging, National Institutes of Health, Baltimore, Maryland; Luigi Ferrucci, Clinical Research Branch, National Institute on Aging, Baltimore, Maryland; Stuart Pickering-Brown, Institute of Brain, Behaviour and Mental Health, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK; Andrew B. Singleton, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; John Hardy, University College London, Department of Molecular Neuroscience, London, UK; and Parastoo Momeni, Laboratory of Neurogenetics, Department of Internal Medicine, Texas Tech University Health Science Center, Lubbock.

The International Parkinson's Disease Genomics Consortium members include Mike A. Nalls, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Vincent Plagnol, University College

London Genetics Institute, London, UK; Dena G Hernandez, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, and Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; Manu Sharma, Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and German Center for Neurodegenerative Diseases, Tübingen, Germany; Una-Marie Sheerin, Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; Mohamad Saad, INSERM U563, Le Centre de Physiopathologie de Toulouse-Purpan, and Paul Sabatier University, Toulouse, France; Javier Simón-Sánchez, Department of Clinical Genetics, Section of Medical Genomics, Vrije Universiteit University Medical Centre, Amsterdam, the Netherlands; Claudia Schulte, Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany; Suzanne Lesage, INSERM, UMR_S975 (formerly UMR_S679), Université Pierre et Marie Curie-Paris, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, and CNRS, Paris, France; Sigurlaug Sveinbjörnsdóttir, Department of Neurology, Landspítali University Hospital, Reykjavík, Iceland, Department of Neurology, Mid Essex Hospital Services National Health Service Trust Broomfield Hospital, Chelmsford, Essex, UK, and Queen Mary College, University of London, London, UK; Sampath Arepalli, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Roger Barker, Department of Neurology, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK; Yoav Ben-Shlomo, School of Social and Community Medicine, University of Bristol, Bristol, UK; Henk W Berendse, Department of Neurology and Alzheimer Center, Vrije Universiteit University Medical Center, Amsterdam, the Netherlands; Daniela Berg, Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and German Center for Neurodegenerative Diseases, Tübingen, Germany; Kailash Bhatia, Department of Motor Neuroscience, University College London Institute of Neurology, London, UK; Rob M. A. de Bie, Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; Alessandro Biffi, Center for Human Genetic Research and Department of Neurology, Massachusetts General Hospital, Boston, and Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts; Bas Bloem, Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; Zoltan Bochdanovits, Department of Clinical Genetics, Section of Medical Genomics, Vrije Universiteit University Medical Center, Amsterdam, the Netherlands; Michael Bonin, Department of Medical Genetics, Institute of Human Genetics, University of Tübingen, Tübingen, Germany; Jose M. Bras, Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; Kathrin Brockmann, Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and German Center for Neurodegenerative Diseases, Tübingen, Germany; Janet Brooks, Laboratory of Neurogenetics, National Institute on Aging,

National Institutes of Health, Bethesda, Maryland; David J. Burn, Newcastle University Clinical Ageing Research Unit, Campus for Ageing and Vitality, Newcastle upon Tyne, UK; Gavin Charlesworth, Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; Honglei Chen, Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Durham, North Carolina; Patrick F. Chinnery, Neurology M4104, The Medical School, Framlington Place, Newcastle upon Tyne, UK; Sean Chong, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Carl E. Clarke, School of Clinical and Experimental Medicine, University of Birmingham, and Department of Neurology, City Hospital, Sandwell and West Birmingham Hospitals National Health Service Trust, Birmingham, UK; Mark R. Cookson, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; J. Mark Cooper, Department of Clinical Neurosciences, University College London Institute of Neurology, London, UK; Jean Christophe Corvol, INSERM, UMR_S975, Université Pierre et Marie Curie-Paris, CNRS, and INSERM CIC-9503, Hôpital Pitié-Salpêtrière, Paris, France; Carl Counsell, University of Aberdeen, Division of Applied Health Sciences, Population Health Section, Aberdeen, UK; Philippe Damier, CHU Nantes, CIC0004, Service de Neurologie, Nantes, France; Jean-François Dartigues, INSERM U897, Université Victor Segalen, Bordeaux, France; Panos Deloukas, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, UK; Günther Deuschl, Klinik für Neurologie, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Christian-Albrechts-Universität Kiel, Kiel, Germany; David T. Dexter, Parkinson's Disease Research Group, Faculty of Medicine, Imperial College London, London, UK; Karin D. van Dijk, Department of Neurology and Alzheimer Center, Vrije Universiteit University Medical Center, Amsterdam, the Netherlands; Allissa Dillman, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Frank Durif, Service de Neurologie, Hôpital Gabriel Montpied, Clermont-Ferrand, France; Alexandra Dürr, INSERM, UMR_S975, Université Pierre et Marie Curie-Paris, CNRS, and AP-HP, Pitié-Salpêtrière Hospital, Paris, France; Sarah Edkins, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, UK; Jonathan R. Evans, Cambridge Centre for Brain Repair, Cambridge, UK; Thomas Foltynie, University College London Institute of Neurology, London, UK; Jing Dong, Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Durham, North Carolina; Michelle Gardner, Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; J. Raphael Gibbs, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, and Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; Alison Goate, Department of Psychiatry, Department of Neurology, Washington University School of Medicine, St Louis, Missouri; Emma Gray, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, UK; Rita Guerreiro, Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK;

Clare Harris, University of Aberdeen, Aberdeen, UK; Jacobus J. van Hilten, Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands; Albert Hofman, Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands; Albert Hollenbeck, AARP, Washington DC; Janice Holton, Queen Square Brain Bank for Neurological Disorders, University College London Institute of Neurology, London, UK; Michele Hu, Department of Clinical Neurology, John Radcliffe Hospital, Oxford, UK; Xuemei Huang, Departments of Neurology, Radiology, Neurosurgery, Pharmacology, Kinesiology, and Bioengineering, Pennsylvania State University, Milton S. Eisenhower Medical Center, Hershey; Isabel Wurster, Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and German Center for Neurodegenerative Diseases, Tübingen, Germany; Walter Mätzler, Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and German Center for Neurodegenerative Diseases, Tübingen, Germany; Gavin Hudson, Neurology M4104, The Medical School, Newcastle upon Tyne, UK; Sarah E. Hunt, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, UK; Johanna Huttenlocher, deCODE genetics, Reykjavík, Iceland; Thomas Illig, Institute of Epidemiology, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany; Pálmi V. Jónsson, Department of Geriatrics, Landspítali University Hospital, Reykjavík, Iceland; Jean-Charles Lambert, INSERM U744, and Institut Pasteur de Lille, Université de Lille Nord, Lille, France; Cordelia Langford, Cambridge Centre for Brain Repair, Cambridge, UK; Andrew Lees (Queen Square Brain Bank for Neurological Disorders), London, UK; Peter Lichtner, Institute of Human Genetics, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany; Patricia Limousin, Institute of Neurology, Sobell Department, Unit of Functional Neurosurgery, London, UK; Grisel Lopez, Section on Molecular Neurogenetics, Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland; Delia Lorenz, Klinik für Neurologie, Universitätsklinikum Schleswig-Holstein, Kiel, Germany; Alisdair McNeill, Department of Clinical Neurosciences, University College London Institute of Neurology, London, UK; Catriona Moorby, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK; Matthew Moore, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Huw R. Morris, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK; Karen E. Morrison, School of Clinical and Experimental Medicine, University of Birmingham, and Neurosciences Department, Queen Elizabeth Hospital, University Hospitals Birmingham National Health Service Foundation Trust, Birmingham, UK; Ese Mudanohwo, Neurogenetics Unit, University College London Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK; Sean S. O'Sullivan, Queen Square Brain Bank for Neurological Disorders, London, UK; Justin Pearson, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK; Joel S.

Perlmutter, Department of Neurology, Radiology, and Neurobiology at Washington University, St Louis, Missouri; Hjörvar Pétursson, deCODE genetics, Reykjavik, Iceland, and Department of Medical Genetics, Institute of Human Genetics, University of Tübingen, Tübingen, Germany; Pierre Pollak, Service de Neurologie, CHU de Grenoble, Grenoble, France; Bart Post, Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; Simon Potter, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, UK; Bernard Ravina, Translational Neurology, Biogen Idec, Cambridge, Massachusetts; Tamas Revesz, Queen Square Brain Bank for Neurological Disorders, London, UK; Olaf Riess, Department of Medical Genetics, Institute of Human Genetics, University of Tübingen, Tübingen, Germany; Fernando Rivadeneira, Departments of Epidemiology and Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands; Patrizia Rizzu, Department of Clinical Genetics, Section of Medical Genomics, Vrije Universiteit University Medical Centre, Amsterdam, the Netherlands; Mina Ryten, Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; Stephen Sawcer, University of Cambridge, Department of Clinical Neurosciences, Addenbrooke's Hospital, Cambridge, UK; Anthony Schapira, Department of Clinical Neurosciences, University College London Institute of Neurology, London, UK; Hans Scheffer, Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; Karen Shaw, Queen Square Brain Bank for Neurological Disorders, London, UK; Ira Shoulson, Department of Neurology, University of Rochester, Rochester, New York; Ellen Sidransky, Section on Molecular Neurogenetics, Medical Genetics Branch National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland; Colin Smith, Department of Pathology, University of Edinburgh, Edinburgh, UK; Chris C. A. Spencer, Wellcome Trust Centre for Human Genetics, Oxford, UK; Hreinn Stefánsson, deCODE genetics, Reykjavik, Iceland; Francesco Bettella, deCODE genetics, Reykjavik, Iceland; Joanna D. Stockton, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK; Amy Strange, Wellcome Trust Centre for Human Genetics, London, UK; Kevin Talbot, University of Oxford, Department of Clinical Neurology, John Radcliffe Hospital, Oxford, UK; Carlie M. Tanner, Clinical Research Department, The Parkinson's Institute and Clinical Center, Sunnyvale, California; Avazeh Tashakkori-Ghanbaria, Wellcome Trust Sanger Institute, Cambridge, UK; François Tison, Service de Neurologie, Hôpital Haut-Lévêque, Pessac, France; Daniah Trabzuni, Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; Bryan J. Traynor, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; André G. Uitterlinden, Departments of Epidemiology and Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands; Daan Velseboer, Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; Marie Vidailhet, INSERM, UMR_S975, Université Pierre et Marie Curie-Paris, CNRS, UMR 7225, Paris, France; Robert Walker, Department of Pathology, University of Edinburgh, Edinburgh, UK; Bart van de Warrenburg, Department of Neurology,

Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; Miridhu Wickremaratchi, Department of Neurology, Cardiff University, Cardiff, UK; Nigel Williams, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK; Caroline H. Williams-Gray, Department of Neurology, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK; Sophie Winder-Rhodes, Department of Psychiatry and Medical Research Council and Wellcome Trust Behavioural and Clinical Neurosciences Institute, University of Cambridge, Cambridge, UK; Kári Stefánsson, deCODE genetics, Reykjavik, Iceland; Maria Martinez, INSERM UMR 1043, and Paul Sabatier University, Toulouse, France; Nicholas W. Wood, University College London Genetics Institute, and Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; John Hardy, Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; Peter Heutink, Department of Clinical Genetics, Section of Medical Genomics, Vrije Universiteit University Medical Centre, Amsterdam, the Netherlands; Alexis Brice, INSERM, UMR_S975, Université Pierre et Marie Curie-Paris, CNRS, UMR 7225, AP-HP, Pitié-Salpêtrière Hospital, Paris, France; Thomas Gasser, Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany; and Andrew B. Singleton, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland.

The International Collaboration for Frontotemporal Dementia members include Vivianna M Van Deerlin, Center for Neurodegenerative Disease Research and Institute on Aging, University of Pennsylvania Perelman School of Medicine, Philadelphia; Patrick MA Sleiman, Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Maria Martinez-Lage, Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia; Alice Chen-Plotkin, Department of Neurology, University of Pennsylvania, Philadelphia; Li-San Wang, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia; Neill R. Graff-Radford, Department of Neurology, Mayo Clinic, Jacksonville, Florida; Dennis W. Dickson, Department of Neuroscience, Mayo Clinic, Jacksonville, Florida; Rosa Rademakers, Department of Neuroscience, Mayo Clinic, Jacksonville, Florida; Bradley F. Boeve, Department of Neurology, Mayo Clinic and Foundation, and Mayo Clinic Alzheimer's Disease Research Center, Mayo Clinic and Foundation, Rochester, Minnesota; Murray Grossman, Department of Neurology, University of Pennsylvania Health System, Philadelphia; Steven E. Arnold, Department of Psychiatry, Center for Neurobiology and Behavior, University of Pennsylvania School of Medicine, Philadelphia; David M. A. Mann, Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Salford Royal Hospital, Salford UK; Stuart M. Pickering-Brown, Division of Neuroscience and Experimental Psychology, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; Harro Seelaar, Department of Neurology, Erasmus Medical Center,

Rotterdam, the Netherlands; Peter Heutink, Department of Clinical Genetics, Vrije Universiteit Medical Center, Section Medical Genomics, Amsterdam, the Netherlands; John C. van Swieten, Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands; Jill R. Murrell, Indiana Alzheimer Disease Center, Indiana University School of Medicine, and Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis; Bernardino Ghetti, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis; Salvatore Spina, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis; Jordan Grafman, Department of Psychiatry, Feinberg School of Medicine and Department of Psychology, Northwestern University, Weinberg College of Arts and Sciences, Chicago, Illinois; John Hodges, Brain and Mind Centre, University of Sydney Medical School, Sydney, Australia; Maria Grazia Spillantini, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK; Sid Gilman, Department of Neurology, University of Michigan, Ann Arbor; Andrew P. Lieberman, Department of Pathology, University of Michigan Medical School, Ann Arbor; Jeffrey A. Kaye, Department of Neurology, Oregon Health & Science University, Portland; Randall L. Woltjer, Department of Neurology, Oregon Health Science University, and Portland Veterans Affairs Medical Center, Portland; Eileen H. Bigio, Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, Illinois; Marsel Mesulam, Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois; Safa al-Sarraj, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, Oxford, UK; Claire Troakes, Department of Clinical Neuroscience, Medical Research Council Centre for Neurodegeneration Research, King's College London, London, UK; Roger N. Rosenberg, Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas; Charles L. White III, Department of Pathology, University of Texas Southwestern Medical Center, Dallas; Isidro Ferrer, Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain; Albert Lladó, Alzheimer's Disease and Other Cognitive Disorders Unit, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; Manuela Neumann, Department of Neuropathology, German Center for Neurodegenerative Diseases, University of Tübingen, Tübingen, Germany; Hans A. Kretschmar, Institut für Neuropathologie, Ludwig-Maximilians-Universität and Brain Net Germany, Munich, Germany; Christine Marie Hulette, Department of Pathology, Duke University Health Sciences Center, Durham, North Carolina; Kathleen A. Welsh-Bohmer, Department of Psychiatry, Duke University Health Sciences Center, and Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University Health Sciences Center, Durham, North Carolina; Bruce L. Miller, Department of Neurology, Memory and Aging Center, University of California, San Francisco; Ainhoa Alzualde, Neurogenetic Unit, Instituto Biodonostia, San Sebastián, Spain; Adolfo Lopez de Munain, Servicio de Neurología, Hospital Donostia, San Sebastián, Spain; Ann C. McKee, Departments of Neurology and Pathology, Boston University School of Medicine, Boston,

Massachusetts, and Bedford Veterans Administration Medical Center, Geriatric Research, Education, and Clinical Center, Bedford Massachusetts; Marla Gearing, Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia; Allan I. Levey, Department of Neurology, Emory University School of Medicine, and Alzheimer's Disease Research Center, Emory University School of Medicine, Atlanta, Georgia; James J. Lah, Department of Neurology, Emory University School of Medicine, Atlanta, Georgia; John Hardy, Reta Lila Weston Institute, University College London Institute of Neurology, London, UK; Jonathan D. Rohrer, Department of Neurodegenerative Disease, Dementia Research Centre, University College London Institute of Neurology, University College London, London, UK; Tammayn Lashley, Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK; Ian R. A. Mackenzie, Department of Pathology, University of British Columbia, Vancouver, British Columbia, Canada; Howard H. Feldman, Division of Neurology, Vancouver General Hospital and the University of British Columbia, Vancouver, British Columbia, Canada; Ronald L. Hamilton, Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania; Steven T. Dekosky, Department of Neurology, University of Virginia School of Medicine, Charlottesville; Julie van der Zee, Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, and Institute Born-Bunge and University of Antwerp, Antwerpen, Belgium; Samir Kumar-Singh, Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, and Institute Born-Bunge and University of Antwerp, Antwerpen, Belgium; Christine Van Broeckhoven, Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, and Institute Born-Bunge and University of Antwerp, Antwerpen, Belgium; Richard Mayeux, Department of Neurology and Sergievsky Center, Columbia University, New York, New York; Jean Paul G. Vonsattel, Department of Pathology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, New York; Juan C. Troncoso, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland; Jillian J. Kril, Disciplines of Medicine and Pathology, University of Sydney, Sydney, Australia; John B. J. Kwok, Prince of Wales Medical Research Institute, Sydney, Australia; Glenda M. Halliday, Prince of Wales Medical Research Institute, Sydney, Australia, and University of New South Wales, New South Wales, Australia; Thomas D. Bird, Geriatrics Research Education and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, Washington; Paul G. Ince, Department of Neuroscience, University of Sheffield, Sheffield, UK; Pamela J. Shaw, Department of Neuroscience, University of Sheffield, Sheffield, UK; Nigel J. Cairns, Alzheimer's Disease Research Center, Washington University School of Medicine, and Department of Neurology, Washington University School of Medicine, St Louis, Missouri; John C. Morris, Alzheimer's Disease Research Center, Washington University School of Medicine, and Department of Neurology, Washington University School of Medicine, St Louis, Missouri; Catriona Ann McLean, Department of Anatomical Pathology, The Alfred Hospital, Melbourne, Australia; Charles DeCarli, Alzheimer's Disease Center, Imaging of Dementia and Aging Laboratory, Department of

Neurology, Center for Neuroscience, University of California at Davis, Sacramento; William G. Ellis, Department of Pathology, University of California at Davis, Sacramento; Stefanie H. Freeman, C. S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital and Harvard Medical School, Boston; Matthew P. Frosch, C. S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital and Harvard Medical School, Boston; John H. Growdon, C. S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital and Harvard Medical School, Boston; Daniel P. Perl, Department of Pathology, Mount Sinai School of Medicine, New York, New York; Mary Sano, Department of Pathology, Mount Sinai School of Medicine, New York, New York; David A. Bennett, Rush Alzheimer's Disease Center, Rush University Medical Center, Sun City, Arizona; Julie A. Schneider, Rush Alzheimer's Disease Center, Rush University Medical Center, Sun City, Arizona; Thomas G. Beach, Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, Arizona; Eric M. Reiman, Banner Alzheimer's Institute, Translational Genomics Research Institute, University of Arizona, Phoenix, Arizona; Bryan K. Woodruff, Mayo Clinic Arizona, Scottsdale, Arizona; Jeffrey Cummings, Mary S. Easton Center for Alzheimer's Disease Research, Los Angeles, California; Harry V. Vinters, Department of Pathology and Laboratory Medicine, Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, California; Carol A. Miller, Keck School of Medicine, University of Southern California, Los Angeles; Helena C. Chui, Keck School of Medicine, University of Southern California, Los Angeles; Irina Alafuzoff, Department of Genetics and Pathology, Uppsala University, Uppsala, Sweden, Department of Clinical Medicine, Kuopio University, Kuopio, Finland, and Department of Neurology, Kuopio University, Kuopio, Finland; Päivi Hartikainen, Department of Neurology, Kuopio University, Kuopio, Finland; Danielle Seilhean, UPMC- Univ Paris 06 and APHP, Paris, France; Douglas Galasko, Department of Neurosciences, University of California, San Diego; Eliezer Masliah, Department of Neurosciences, and Department of Pathology, University of California San Diego, La Jolla; Carl W. Cotman, Department of Neurology, University of California, Irvine; M. Teresa Tuñón, Hospital de Navarra Pathology Department, and Brain Bank of Navarra, Spain; M. Cristina Caballero Martínez, Brain Bank of Navarra, and Biomedical Research Center, Navarra Health Service-Osasunbidea, Spain; David G. Munoz, Department of Laboratory Medicine and Pathobiology, Li Ka Shing Knowledge Institute of St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; Steven L. Carroll, Department of Pathology, University of Alabama at Birmingham; Daniel Marson, Department of Neurology, University of Alabama at Birmingham; Peter F. Riederer, Clinical Neurochemistry Clinic and Policlinic of Psychiatry, Psychosomatic and Psychotherapy of the University of Wuerzburg, Wuerzburg, Germany; Nenad Bogdanovic, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Hudding University Hospital, Stockholm, Sweden; Gerard D. Schellenberg, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia; Hakon Hakonarson, Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; John Q. Trojanowski, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia; and

Virginia M.-Y. Lee, Center for Neurodegenerative Disease Research and Institute on Aging, University of Pennsylvania Perelman School of Medicine, Philadelphia.

Additional Contributions: Jan Veldink, PhD, University Medical Center Utrecht, provided summary statistics and thoughtful discussion of the manuscript. He was not compensated for his contribution. We thank the International FTD-GWAS Consortium, the International Collaboration for Frontotemporal Dementia, and International Parkinson's Disease Genomic Consortium for providing summary statistics data for these analyses (eAppendix 2 in the Supplement).

REFERENCES

- Ferrari R, Kapogiannis D, Huey ED, Momeni P. FTD and ALS: a tale of two diseases. *Curr Alzheimer Res.* 2011;8(3):273-294.
- Cairns NJ, Bigio EH, Mackenzie IRA, et al; Consortium for Frontotemporal Lobar Degeneration. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol.* 2007;114(1):5-22.
- Gitcho MA, Bigio EH, Mishra M, et al. TARDBP 3'-UTR variant in autopsy-confirmed frontotemporal lobar degeneration with TDP-43 proteinopathy. *Acta Neuropathol.* 2009;118(5):633-645.
- Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science.* 2006;314(5796):130-133.
- Rademakers R, Eriksen JL, Baker M, et al. Common variation in the miR-659 binding-site of GRN is a major risk factor for TDP43-positive frontotemporal dementia. *Hum Mol Genet.* 2008;17(23):3631-3642.
- Renton AE, Majounie E, Waite A, et al; ITALSGEN Consortium. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron.* 2011;72(2):257-268.
- DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron.* 2011;72(2):245-256.
- Yokoyama JS, Wang Y, Schork AJ, et al; Alzheimer's Disease Neuroimaging Initiative. Association between genetic traits for immune-mediated diseases and Alzheimer disease. *JAMA Neurol.* 2016;73(6):691-697.
- Yokoyama JS, Karch CM, Fan CC, et al; International FTD-Genomics Consortium (IFGC). Shared genetic risk between corticobasal degeneration, progressive supranuclear palsy, and frontotemporal dementia. *Acta Neuropathol.* 2017;133(5):825-837.
- Desikan RS, Schork AJ, Wang Y, et al; ADNI, ADGC, GERAD, CHARGE and IPDGC Investigators. Genetic overlap between Alzheimer's disease and Parkinson's disease at the MAPT locus. *Mol Psychiatry.* 2015;20(12):1588-1595.
- Ferrari R, Wang Y, Vandrovicova J, et al; International FTD-Genomics Consortium (IFGC); International Parkinson's Disease Genomics Consortium (IPDGC); International Genomics of Alzheimer's Project (IGAP). Genetic architecture of

- sporadic frontotemporal dementia and overlap with Alzheimer's and Parkinson's diseases. *J Neurol Neurosurg Psychiatry*. 2017;88(2):152-164.
12. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al; European Alzheimer's Disease Initiative (EADI); Genetic and Environmental Risk in Alzheimer's Disease; Alzheimer's Disease Genetic Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet*. 2013;45(12):1452-1458.
 13. Nalls MA, Plagnol V, Hernandez DG, et al; International Parkinson Disease Genomics Consortium. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet*. 2011;377(9766):641-649.
 14. van Rheenen W, Shatunov A, Dekker AM, et al; PARALS Registry; SLALOM Group; SLAP Registry; FALS Sequencing Consortium; SLAGEN Consortium; NNIPPS Study Group. Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. *Nat Genet*. 2016;48(9):1043-1048.
 15. Van Deerlin VM, Sleiman PM, Martinez-Lage M, et al. Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions. *Nat Genet*. 2010;42(3):234-239.
 16. Kouri N, Ross OA, Dombroski B, et al. Genome-wide association study of corticobasal degeneration identifies risk variants shared with progressive supranuclear palsy. *Nat Commun*. 2015; 6:7247.
 17. Höglinger GU, Melhem NM, Dickson DW, et al; PSP Genetics Study Group. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. *Nat Genet*. 2011;43(7):699-705.
 18. Ferrari R, Hernandez DG, Nalls MA, et al. Frontotemporal dementia and its subtypes: a genome-wide association study. *Lancet Neurol*. 2014;13(7):686-699.
 19. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis: subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. *J Neurol Sci*. 1994;124(suppl):96-107.
 20. Andreassen OA, Djurovic S, Thompson WK, et al; International Consortium for Blood Pressure GWAS; Diabetes Genetics Replication and Meta-analysis Consortium; Psychiatric Genomics Consortium Schizophrenia Working Group. Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. *Am J Hum Genet*. 2013;92(2):197-209.
 21. Andreassen OA, Thompson WK, Schork AJ, et al; Psychiatric Genomics Consortium (PGC); Bipolar Disorder and Schizophrenia Working Groups. Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional false discovery rate. *PLoS Genet*. 2013;9(4):e1003455.
 22. Desikan RS, Schork AJ, Wang Y, et al; Inflammation working group, IGAP and DemGene Investigators. Polygenic overlap between C-reactive protein, plasma lipids, and Alzheimer disease. *Circulation*. 2015;131(23):2061-2069.
 23. Ramasamy A, Trabzuni D, Guelfi S, et al; UK Brain Expression Consortium; North American Brain Expression Consortium. Genetic variability in the regulation of gene expression in ten regions of the human brain. *Nat Neurosci*. 2014;17(10):1418-1428.
 24. Takata A, Matsumoto N, Kato T. Genome-wide identification of splicing QTLs in the human brain and their enrichment among schizophrenia-associated loci. *Nat Commun*. 2017;8:14519.
 25. Dangond F, Hwang D, Camelo S, et al. Molecular signature of late-stage human ALS revealed by expression profiling of postmortem spinal cord gray matter. *Physiol Genomics*. 2004;16(2):229-239.
 26. Karch CM, Prudencio M, Winkler DD, Hart PJ, Borchelt DR. Role of mutant SOD1 disulfide oxidation and aggregation in the pathogenesis of familial ALS. *Proc Natl Acad Sci U S A*. 2009;106(19):7774-7779.
 27. Lukas TJ, Luo WW, Mao H, Cole N, Siddique T. Informatics-assisted protein profiling in a transgenic mouse model of amyotrophic lateral sclerosis. *Mol Cell Proteomics*. 2006;5(7):1233-1244.
 28. Allen M, Carrasquillo MM, Funk C, et al. Human whole genome genotype and transcriptome data for Alzheimer's and other neurodegenerative diseases. *Sci Data*. 2016;3:160089.
 29. Chen-Plotkin AS, Geser F, Plotkin JB, et al. Variations in the progranulin gene affect global gene expression in frontotemporal lobar degeneration. *Hum Mol Genet*. 2008;17(10):1349-1362.
 30. Kamburov A, Pentchev K, Galicka H, Wierling C, Lehrach H, Herwig R. ConsensusPathDB: toward a more complete picture of cell biology. *Nucleic Acids Res*. 2011;39(Database issue):D712-D717.
 31. Kamburov A, Stelzl U, Lehrach H, Herwig R. The ConsensusPathDB interaction database: 2013 update. *Nucleic Acids Res*. 2013;41(Database issue): D793-D800.
 32. Trabzuni D, Wray S, Vandrovicova J, et al. *MAPT* expression and splicing is differentially regulated by brain region: relation to genotype and implication for tauopathies. *Hum Mol Genet*. 2012;21(18):4094-4103.
 33. Auton A, Brooks LD, Durbin RM, et al; 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature*. 2015;526(7571):68-74.
 34. Jones AR, Woollacott I, Shatunov A, et al. Residual association at *C9orf72* suggests an alternative amyotrophic lateral sclerosis-causing hexanucleotide repeat. *Neurobiol Aging*. 2013;34(9):2234.e1-2234.e7.
 35. Dobson-Stone C, Hallupp M, Bartley L, et al. *C9ORF72* repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts. *Neurology*. 2012;79(10):995-1001.
 36. Ng ASL, Tan EK. Intermediate *C9orf72* alleles in neurological disorders: does size really matter? *J Med Genet*. 2017;54(9):591-597.
 37. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature*. 1998;393(6686):702-705.
 38. Zhang CC, Zhu JX, Wan Y, et al. Meta-analysis of the association between variants in *MAPT* and neurodegenerative diseases. *Oncotarget*. 2017;8(27):44994-45007.
 39. Beevers JE, Lai MC, Collins E, et al. *MAPT* genetic variation and neuronal maturity alter isoform expression affecting axonal transport in iPSC-derived dopamine neurons. *Stem Cell Reports*. 2017;9(2):587-599.
 40. Tang F, Wang B, Li N, et al. RNF185, a novel mitochondrial ubiquitin E3 ligase, regulates autophagy through interaction with BNIP1. *PLoS One*. 2011;6(9):e24367.
 41. Nakajima K, Hirose H, Taniguchi M, et al. Involvement of *BNIP1* in apoptosis and endoplasmic reticulum membrane fusion. *EMBO J*. 2004;23(16):3216-3226.
 42. Youle RJ, Narendra DP. Mechanisms of mitophagy. *Nat Rev Mol Cell Biol*. 2011;12(1):9-14.
 43. Taylor JP, Brown RH Jr, Cleveland DW. Decoding ALS: from genes to mechanism. *Nature*. 2016;539(7628):197-206.
 44. Wong YC, Holzbaur EL. Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. *Proc Natl Acad Sci U S A*. 2014; 111(42):E4439-E4448.
 45. Cirulli ET, Lasseigne BN, Petrovski S, et al; FALS Sequencing Consortium. Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. *Science*. 2015;347(6229):1436-1441.
 46. Freischmidt A, Wieland T, Richter B, et al. Haploinsufficiency of *TBKT* causes familial ALS and fronto-temporal dementia. *Nat Neurosci*. 2015;18(5):631-636.
 47. Ehrlich M, Hallmann AL, Reinhardt P, et al. Distinct neurodegenerative changes in an induced pluripotent stem cell model of frontotemporal dementia linked to mutant tau protein. *Stem Cell Reports*. 2015;5(1):83-96.
 48. Hallmann AL, Araúzo-Bravo MJ, Mavrommatis L, et al. Astrocyte pathology in a human neural stem cell model of frontotemporal dementia caused by mutant tau protein. *Sci Rep*. 2017;7:42991.
 49. Stoica R, Paillusson S, Gomez-Suaga P, et al. ALS/FTD-associated FUS activates GSK-3 β to disrupt the VAPB-PTPIP51 interaction and ER-mitochondria associations. *EMBO Rep*. 2016;17(9):1326-1342.
 50. Ferrari R, Forabosco P, Vandrovicova J, et al; UK Brain Expression Consortium (UKBEC). Frontotemporal dementia: insights into the biological underpinnings of disease through gene co-expression network analysis. *Mol Neurodegener*. 2016;11:21.
 51. Ling SC, Polyomenidou M, Cleveland DW. Converging mechanisms in ALS and FTD: disrupted RNA and protein homeostasis. *Neuron*. 2013;79(3):416-438.
 52. Stutzbach LD, Xie SX, Naj AC, et al; PSP Genetics Study Group. The unfolded protein response is activated in disease-affected brain regions in progressive supranuclear palsy and Alzheimer's disease. *Acta Neuropathol Commun*. 2013;1:31.