Identification of common variants influencing risk of the tauopathy Progressive Supranuclear Palsy

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Competing Financial Interests T.G. serves as an editorial board member of Movement Disorders and Parkinsonism and Related Disorders and is funded by Novartis Pharma, the Federal Ministry of Education and Research (BMBF) (NGFN-Plus and ERA-Net NEURON), the Helmholtz Association (HelmH, Helmholtz Alliance for Health in an Ageing Society) and the European Community (MeFoPa, MeddelnDelan Form of Parkinsonism). T.G. received speakers honoraria from Novartis, Merck-Serono, Schwarz Pharma, Boehringer Ingelheim and Valeant Pharma and royalties for his consulting activities from Cefalon Pharma and Merck-Serono. T.G. holds a patent concerning the LRRK2 gene and neurodegenerative disorders. J.H. is consulting for Merck Serono and Eisai. I.Litvan is the founder of the Litvan Neurological Research Foundation, whose mission is to increase awareness, determine the cause/s and search for a cure for neurodegenerative disorders presenting with either parkinsonian or dementia symptoms (501c3).
Progressive supranuclear palsy (PSP) is a movement disorder with prominent tau neuropathology. Brain diseases with abnormal tau deposits are called tauopathies, the most common being Alzheimer’s disease. Environmental causes of tauopathies include repetitive head trauma associated with some sports. To identify common genetic variation contributing to risk for tauopathies, we carried out a genome-wide association study of 1,114 PSP cases and 3,247 controls (Stage 1) followed up by a second stage where 1,051 cases and 3,560 controls were genotyped for Stage 1 SNPs that yielded $P \leq 10^{-3}$. We found significant novel signals ($P < 5 \times 10^{-8}$).
$10^{-8}$) associated with PSP risk at *STX6*, *EIF2AK3*, and *MOBP*. We confirmed two independent variants in *MAPT* affecting risk for PSP, one of which influences *MAPT* brain expression. The genes implicated encode proteins for vesicle-membrane fusion at the Golgi-endosomal interface, for the endoplasmic reticulum unfolded protein response, and for a myelin structural component.

PSP is a rare neurodegenerative movement disorder clinically characterized by falls, axial rigidity, vertical supranuclear gaze palsy, bradykinesia, and cognitive decline. Though PSP is rare (prevalence is 3.1–6.5/100,000\(^1\)), after Parkinson’s disease (PD), PSP is the second most common cause of degenerative parkinsonism\(^2\). PSP is a tauopathy with abnormal accumulation of tau protein within neurons as neurofibrillary tangles (NFTs), primarily in the basal ganglia, diencephalon, and brainstem, with neuronal loss in globus pallidus, subthalamic nucleus and substantia nigra. Abnormal tau also accumulates within oligodendroglia and astrocytes\(^3\). In Alzheimer’s disease (AD), even though all cases have NFTs, A\(\beta\) plaques are closely tied to the primary disease process, and thus AD is a secondary tauopathy. PSP is a primary tauopathy because tau is the major abnormal protein observed. Both environmental insults and inherited factors contribute to the risk of developing tauopathies\(^4\). Repetitive brain trauma, associated with certain sports, can cause chronic traumatic encephalopathy associated with tau deposits\(^5\). Viral encephalitis, associated with subsequent parkinsonism, is also associated with tau neuropathology. In PSP, neurotoxins\(^4\) and low education levels\(^6\) may also contribute to risk. Genetic risk for PSP is in part determined by variants at a 1 Mb inversion polymorphism that contains a number of genes including *MAPT*, the gene that encodes tau\(^7\). The inversion variants are called H1 and H2 “haplotypes”, with H1 conferring risk for PSP\(^8\). H1 also contributes to risk for corticobasal degeneration\(^9,10\) and Guam amyotrophic lateral sclerosis/parkinsonism dementia complex\(^11\), both rare tauopathies. H1 does not contribute to risk for AD. Surprisingly, H1 is also a risk factor for PD\(^12\), a movement disorder with clinical features that overlap those of PSP, yet in PD there are no neuropathologically recognizable tau containing lesions.

We performed a genome wide association (GWA) study of PSP to identify genes that modify risk for this primary tauopathy. We performed a two-stage analysis to maximize efficiency while maintaining power\(^13,14\). For Stage 1 we used only autopsied cases (n = 1,114), thereby essentially eliminating incorrect diagnoses. These were contrasted with 3,287 controls; 96% of cases and 90% of controls were of European ancestry (Table 1, Supplementary Table 1). We assessed association between genotypes at 531,451 single nucleotide polymorphisms (SNPs) and PSP status among subjects of all ancestries (Supplementary Table 2) and those of only European ancestry (Table 2) using an additive model. Results from both ancestry groups were similar. Because our control samples were younger than cases, we compared their allele frequencies at significant and strongly suggestive SNPs to those of older controls (N = 3,816) from three datasets from the NIH repository Database for Genotypes and Phenotypes (Supplementary Table 3). Only SNPs with no significant differences in allele frequencies between old and young controls are presented in Table 2.
Stage 1 P-values ($P_1$) for SNPs in three regions crossed the significance threshold of $P < 5 \times 10^{-8}$ (Table 2, Fig. 1). At 1q25.3, a SNP in STX6 crossed this threshold ($P_1 = 1.8 \times 10^{-9}$). Another SNP at 3p22.1 in MOBP crosses this threshold ($P_1 = 1.0 \times 10^{-9}$). The third region was 17q21.31, in which 58 SNPs had $P_1 < 5 \times 10^{-8}$ (Table 2, Fig. 2a). This focus of association is the approximately 1 Mb H1/H2 inversion polymorphism containing MAPT. 

SNPs for Stage 2 were selected from the original set if they yielded a $P_1 < 10^{-3}$. We assessed 4,099 SNPs for association in 1,051 cases, mostly living subjects clinically diagnosed with PSP (Supplementary Table 4) and 3,560 control subjects, all of European ancestry. We also included 197 ancestry informative markers to evaluate population substructure. Clinically diagnosed PSP is reasonably concordant with autopsy results. We estimated the diagnostic misclassification rate as 12%, which has only a small impact on power (Online Methods).

All three loci associated in Stage 1 were replicated by joint analysis (Table 2, Figs. 1 and 2). Joint analysis revealed two new loci with joint P-values ($P_J$) below the genome-wide significant threshold. One was at 2p11.2, within EIF2AK3 ($P_J = 3.2 \times 10^{-13}$). Another, rs12203592 ($P_J = 6.2 \times 10^{-15}$), at 6p25.3, highlighted IRF4, with a neighboring SNP in EXOC2, rs2493013 ($P_J = 6.0 \times 10^{-7}$); rs2493013 was significant after controlling for rs12203592 at $P < 1 \times 10^{-3}$ (Supplementary Table 5). However, allele frequencies for rs12203592 and rs2493013 in older controls were significantly different from those of our controls (Supplementary Table 3). Curiously, the older control data sets were all significantly different from each other. While rs12203592 alleles frequencies vary widely across Europe, we could not ascribe these fluctuations amongst controls to either ancestry or genotyping artifacts. In the joint analysis, 3 other loci reached suggestive association (an intergenic region at 1q41, $P_J = 2.8 \times 10^{-7}$; BMS1, $P_J = 4.9 \times 10^{-7}$; SLCO1A2, $P_J = 1.9 \times 10^{-7}$; Supplementary Table 6 and Figure 5).

In the MAPT region, most of the PSP-associated SNPs mapped directly or closely onto H1/H2, producing very small P-values (e.g., for rs8070723, $P_1 = 2.1 \times 10^{-51}$, $P_J = 1.5 \times 10^{-116}$). H1 confers risk and 95% of PSP subject chromosomes are H1 compared to 77.5% of control chromosomes. In the Stage 1 autopsy cases, the odds ratio (OR) is 5.5 [confidence interval (C.I.) 4.4 – 6.86, Table 2], which is stronger than the OR for the APOE ε3/ε4 genotype as a risk locus for AD. The OR for the Stage 2 PSP samples was comparable to the Stage 1 OR, evidence that the clinically and autopsy-diagnosed cohorts are similar in composition.

If all of the risk from 17q21.31 were associated with H1/H2, controlling for H1/H2 (using rs8070723 as a proxy) should be sufficient to make association at all other loci in this region non-significant. That is not the case; instead certain SNPs remained associated, with the maximum falling in MAPT (rs242557) (Table 2, Figure 2, Supplementary Table 5). No other 17q21.31 SNPs showed association after controlling for rs8070723 and rs242557 genotypes. SNP rs242557 was previously identified as a key regulatory polymorphism influencing MAPT expression. Note that rs242557 accounts for only part of the total risk associated with H1/H2 (Table 2).
The SNPs used to detect a GWA signal are not necessarily the risk-causing variants. For STX6 and EIF2AK3, there are non-synonymous SNPs in close proximity to and highly correlated with the top GWA SNPs (Supplementary Table 7) making these coding changes candidates for the pathogenic change. To evaluate the possibility that some risk-variants regulate gene expression, we analyzed the correlations between gene expression levels from two brain regions of 387 normal subjects and SNP genotypes for the regions listed in Table 2. Two regions showed strong genotype-expression associations (Fig. 3). SNPs falling in or near MOBP have some effect on MOBP expression, but are more strongly correlated with SLC25A38 expression, which is 70 kb from MOBP (Fig. 3a). This effect on SLC25A38 is seen in cerebellum but is weaker in the frontal cortex.

The second region showing a strong genotype-expression correlation is the MAPT inversion region. SNP alleles across the entire H1/H2 inversion and flanking regions show strong correlation with not only MAPT expression (p = 8.71 × 10\(^{-28}\) for multiple SNPs), but also with ARL17A (P = 9.2 × 10\(^{-22}\)), PLEKHM1 (P = 1.0 × 10\(^{-9}\)), and LRRC37A4 (P = 2.2 × 10\(^{-35}\)). Note that while MAPT expression is correlated with SNPs across the entire inversion region, the SNPs influencing ARL17A are associated with a subset of regional SNPs and these are not identical to the SNPs affecting MAPT expression. Expression of CRHR1 and KIAA1267, genes that are in the inversion region and that flank MAPT, is not correlated with H1/H2 SNPs.

To distinguish between the effects on gene expression of the inversion versus other independent effects, we controlled for H1/H2 as was done for association with PSP (Table 2). After controlling for H1/H2, all significant genotype-expression correlation for MAPT and LRRC37A4 disappears (Fig. 3c) showing that either the orientation of this region or a polymorphism that maps onto H1/H2, determines MAPT expression. In contrast, controlling for H1/H2 has no effect on genotype-expression correlations for ARL17A. Potential eSNPs for ARL17A include rs242557 (Table 2), which is highly associated with PSP but more modestly correlated with ARL17A expression, and rs8079215, which is highly correlated with ARL17A expression but not as strongly with risk for PSP. Statistical modeling of these data produce the following conclusions: haplotypes involving H1 and rs242557 alleles predict a highly significant portion of the variability of ARL17A expression; however, essentially all of that variance can be explained by alleles at rs8079215, which are correlated with H1/H2 and rs242557 alleles; and that alleles at rs8079215 cannot predict risk for PSP independent of H1/H2 status even though they are excellent predictors of ARL17A expression. In sum, risk for PSP does not rise and fall with ARL17A expression. The global MAPT brain region expression analyzed here does not explain how rs242557 alleles confer risk to PSP. Yet this SNP or a correlated polymorphism is assumed to have a regulatory effect because there are no coding variants in MAPT brain isoforms that are candidate pathogenic variants. One possible explanation is that rs242557 alleles could affect alternative splicing without altering total MAPT expression levels\(^{22,23}\).

Because AD and PSP are tauopathies, and because H1 is a shared risk factor for PSP and PD, we determined whether any confirmed AD\(^{24–28}\) or PD\(^{29}\) loci also produced suggestive evidence for PSP association (Supplementary Table 8). Besides the overlap between PD and PSP at MAPT, the single noteworthy result was from rs2075650 in TOMM40 that yielded P\(_J\).
for association with PSP. \textit{TOMM40} is adjacent to \textit{APOE} and \textit{rs2075650} tags the AD risk allele, \textit{e4}, in \textit{APOE}. The effect in PSP is opposite that seen in AD: \textit{e4} frequency is elevated in AD and diminished in PSP (for \textit{rs2075650}, the estimated MAF in cases is 0.11 \textit{versus} 0.15 in both our young and older controls; $r^2$ between \textit{rs2075650} and \textit{e4} is 0.33).

Our work suggests a number of intriguing insights into PSP. One comes from \textit{EIF2AK3}, a gene that encodes PERK, a component of the endoplasmic reticulum (ER) unfolded protein response (UPR). When excess unfolded proteins accumulate in the ER, PERK is activated and protein synthesis is inhibited allowing the ER to clear mis-folded proteins and return to homeostasis. The UPR is active in PSP\textsuperscript{30}, AD\textsuperscript{31}, and PD\textsuperscript{32}. In PSP, activated PERK is in neurons, oligodendrocytes, and astrocytes\textsuperscript{30}. In AD, activated UPR components are found in pre-tangle neurons in a number of brain regions\textsuperscript{31}. In PD, UPR activation occurs in neuromelanin containing dopaminergic neurons in the substantia nigra\textsuperscript{32}. How the UPR contributes to PSP pathogenesis is unclear because the primary mis-folded protein in PSP, \textit{tau}, is not a secreted protein and thus is not expected to traffic through the ER.

The PSP susceptibility gene \textit{STX6} encodes syntaxin 6 (Stx6), a SNARE class protein. SNARE proteins are part of the cellular machinery that catalyzes the fusion of vesicles with membranes\textsuperscript{33}. Stx6 is localized to the trans-Golgi network and endosomal structures\textsuperscript{34}. Since our work implicates ER-stress in PSP pathogenesis, genetic variation at \textit{STX6} could influence movement of mis-folded proteins from the ER to lysosomes \textit{via} the endosomal system.

\textit{MOBP} (\textit{Pj} = 1 \times 10^{-16}), like the myelin basic protein gene (\textit{MBP}), encodes a protein (MOBP) that is produced by oligodendrocytes and is present in the major dense line of CNS myelin. MOBP is highly expressed in the white matter of the medulla, pons, cerebellum, and midbrain\textsuperscript{35}, regions affected in PSP. Our findings suggest that myelin dysfunction or oligodendrocyte mis-function contributes to PSP pathogenesis.

Our work generates a testable translational hypothesis based on the results for \textit{EIF2AK3}. Our work suggests that perturbation of the UPR can influence PSP risk, and that the UPR is not just a downstream consequence of neurodegeneration. Thus pharmacologic modulation of the UPR is a potential therapeutic strategy for PSP\textsuperscript{36,37}.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgements**

We thank the patients and their families that participated in this study. This work was funded by grants from the CurePSP Foundation, the Peebler PSP Research Foundation, and National Institutes on Health (NIH) grants R37 AG 11762, R01 PAS-03-092, P50 NS72187, P01 AG17216 [National Institute on Aging(NIA)/NIH], MH057881 and MH077930 [National Institute of Mental Health (NIMH)]. Work was also supported in part by the NIA Intramural Research Program, the German National Genome Research Network (01GS08136-4) and the Deutsche Forschungsgemeinschaft (HO 2402/6-1), Prinzes Beatrix Fonds (J CvS, 01–0128), the Reta Lila Weston Trust and the UK Medical Research Council (Rds: G0501560). The Newcastle Brain Tissue Resource provided tissue and is funded in part by a grant from the UK Medical Research Council (G0400074), by the Newcastle NIHR Biomedical Research Centre in Ageing and Age Related Diseases to the Newcastle upon Tyne Hospitals NHS Foundation Trust, and by a grant from the Alzheimer’s Society and Alzheimer’s Research Trust as part of the Brains for
Dementia Research Project. We acknowledge the contribution of many tissue samples from the Harvard Brain Tissue Resource Center. We also acknowledge the ‘Human Genetic Bank of Patients affected by Parkinson Disease and parkinsonism’ (http://www.parkinson.it/dmabank.html) of the Telethon Genetic Biobank Network, supported by TELETTHON Italy (project n. GTB07001) and by Fondazione Grigioni for the Morbo di Parkinson. The University of Toronto sample collection was supported by grants from Wellcome Trust, Howard Hughes Medical Institute, and the Canadian Institute of Health Research. Brain-Net-Germany is supported by BMBF (01GI0505). Rds, AJL, and JAH are funded by the Reta Lila Weston Trust and the PSP (Europe) Association. Rds is funded by the UK Medical Research Council (Grant G0501560) and Cure PSP+. ZKW is partially supported by the NIH/NINDS IR2SN070276, N057567, P50NS072187, Mayo Clinic Florida (MCF) Research Committee CR programs (MCF #90052030 and MCF #90052030), and the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch (MCF #90052031). The Mayo Clinic College of Medicine would like to acknowledge Matt Baker, Richard Crook, Mariele DeJesus-Hernandez and Nicola Rutherford for their preparation of samples. PP was supported by a grant from the Government of Navarra (“Ayudas para la Realización de Proyectos de Investigación” 2006–2007) and acknowledges the “Iberian Atypical Parkinsonism Study Group Researchers”, i.e. Maria A. Pastor, Maria R. Luquin, Mario Riverol, Jose A. Obeso and Maria C Rodriguez-Oroz (Department of Neurology, Clinica Universitaria de Navarra, University of Navarra, Pamplona, Spain), Marta Blazquez (Neurology Department, Hospital Universitario Central de Asturias, Oviedo, Spain), Adolfo Lopez de Munain, Begoña Indakoetxea, Javier Olaskoaga, Javier Ruiz, José Félix Martí Massó (Servicio de Neurología, Hospital Donostia, San Sebastián, Spain), Victoria Alvarez (Genetics Department, Hospital Universitario Central de Asturias, Oviedo, Spain), Teresa Tuñon (Banco de Tejidos Neurologicos, CIBERNEDE. Hospital de Navarra, Navarra, Spain), Fermín Moreno (Servicio de Neurología, Hospital Ntra. Sra. de la Antigua, Zumarraga, Gipuzkoa, Spain), Ainhoa Alzuide (Neurogenetics Department, Hospital Donostia, San Sebastián, Spain).

The datasets used for older controls were obtained from Database for Genotypes and Phenotypes (dbGap) at http://www.ncbi.nlm.nih.gov/gap. Funding support for the “Genetic Consortium for Late Onset Alzheimer’s Disease” was provided through the Division of Neuroscience, NIA. The Genetic Consortium for Late Onset Alzheimer’s Disease (Study accession number: phs000168.v1.p1) includes a genome-wide association study funded as part of the Division of Neuroscience, NIA. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by Genetic Consortium for Late Onset Alzheimer’s Disease.

Funding support for the “CIDR Visceral Adiposity Study” (Study accession number: phs000169.v1.p1) was provided through the Division of Aging Biology and the Division of Geriatrics and Clinical Gerontology, NIA. The CIDR Visceral Adiposity Study includes a genome-wide association study funded as part of the Division of Aging Biology and the Division of Geriatrics and Clinical Gerontology, NIA. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by Heath ABC Study Investigators. Funding support for the Personalized Medicine Research Project (PMRP) was provided through a cooperative agreement (U01HG004608) with the National Human Genome Research Institute (NHGRI), with additional funding from the National Institute for General Medical Sciences (NIGMS) The samples used for PMRP analyses were obtained with funding from Marshfield Clinic, Health Resources Service Administration Office of Rural Health Policy grant number D1A RH00025, and Wisconsin Department of Commerce Technology Development Fund contract number TDF FY010718. Funding support for genotyping, which was performed at Johns Hopkins University, was provided by the NIH (U01HG004438). Assistance with phenotype harmonization and genotype cleaning was provided by the eMERGE Administrative Coordinating Center (U01HG004603) and the National Center for Biotechnology Information (NCBI). The datasets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/gap through dbGaP accession number phs000170.v1.p1.

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Nat Genet. Author manuscript; available in PMC 2012 January 01.
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Figure 1.
(a) Association results for 1q25.3 $STX6$. (b) Association results for 2p11.2 $EIF2AK3$. (c) Association results for 3p22.1 $MOBP$ regions. $-\log_{10} P$ values are shown for Stages 1 and 2 and the joint analyses. Recombination rate, calculated from the linkage disequilibrium (LD) structure of the region, is derived from Hapmap3 data. LD, encoded by intensity of the colors, is the pairwise LD of the most highly associated SNP at Stage 1 with each of the SNPs in the region. Transcript positions are shown below each graph.
Figure 2.
(a) Association results for the 17q21.31 H1/H2 inversion polymorphism (40,974,015 – 41,926,692 Kb) and flanking segments. (b) Association results for 17q21.31 controlling for H1/H2. Results are shown for Stages 1 and 2 and the joint analyses. Recombination rate, calculated from the linkage disequilibrium (LD) structure of the region, is derived from Hapmap3 data. LD, encoded by intensity of the colors, is the pairwise LD of the most highly associated SNP at Stage 1 with each of the SNPs in the region.
Figure 3.
(a) Association results for the relationship between SNP genotypes and mRNA transcripts from the cerebellum and frontal cortex for the SLC25A38/MOBP region. (b) Association results for the relationship between SNP genotypes and mRNA transcripts from the cerebellum and frontal cortex for the H1/H2 inversion polymorphism region. (c) Association results for the relationship between SNP genotypes and mRNA transcripts from the cerebellum and frontal cortex for the H1/H2 inversion polymorphism region controlling for H1/H2. The color of the circle corresponds to the color assigned each gene and each SNP is
tested against multiple cis transcripts. The data presented here are independent samples from those used previously by Simon-Sanchez et al.12.
Table 1

Characteristics of the samples$^a$

| Cohort                        | Total sample analyzed | Gender (male) | Onset Age | Age-at-death | Disease Duration |
|-------------------------------|-----------------------|---------------|-----------|--------------|-----------------|
|                               | Percent | $^b$ | Mean age | Range | SD (±) | n | Mean age | range | SD (±) | n | Mean duration (years) | range | SD (±) | n |
| PSP stage 1$^c$               | 1,114    | 55   | 599      | 68     | (41–93) | 8.2 | 827     | 75     | 45–99 | 8.0 | 1,070 | 7.4 | 1–21 | 3.2 | 827 |
| PSP stage 1 European Ancestry | 1,069    | 55   | 570      | 68     | (41–93) | 8.3 | 794     | 75     | 45–99 | 8.0 | 1,025 | 7.4 | 1–21 | 3.1 | 794 |
| PSP stage 2$^d$               | 1,051    | 53   | 530      | 65     | (40–91) | 7.3 | 913     | 75     | 57–94 | 7.4 | 118   | 8.0 | <1–18 | 3.3 | 42  |

$^a$Controls were young normal subjects recruited from the Children's Hospital of Philadelphia Health Care Network (See Online Methods for details). These were 3,287 controls for Stage 1 and 3,560 for Stage 2;

$^b$ n, number of samples with available data. Values of n for each type of analysis do not add up to the total samples used because of missing values;

$^c$ Stage 1 consisted of autopsy-confirmed cases.

$^d$ The stage 2 dataset included 130 cases with autopsies. All stage 2 samples (cases and controls) were independent of stage 1 samples.
Table 2

Results from Stage 1, Stage 2, and joint analysis among subjects of European Ancestry: SNPs Significant at $P < 5 \times 10^{-8}$ in the joint analysis

| Chr band | SNP Location (bp) | Gene or nearby gene | Stage 1 | Stage 2 | Joint P |
|----------|-------------------|---------------------|---------|---------|---------|
|          | Rs1411478         | STX6                | MAF Case | MAF Cont | OR/CI | $P_1$ | MAF Case | MAF Cont | OR/CI | $P_2$ | OR/CI | $P_J$ |
| 1q25.3   | 179229155         |                     | 0.50    | 0.42    | 0.73   | 0.65 – 0.81 | 1.8 $\times 10^{-9}$ | 0.46 | 0.43 | 0.85 | 0.77 – 0.94 | 1.5 $\times 10^{-3}$ | 0.79 | 0.74 – 0.85 | 2.3 $\times 10^{-10}$ |
|          | Rs7571971 – 88676716 | EIF2AK3            | 0.31    | 0.26    | 0.75   | 0.66 – 0.84 | 7.4 $\times 10^{-7}$ | 0.31 | 0.25 | 0.75 | 0.67 – 0.83 | 8.7 $\times 10^{-8}$ | 0.75 | 0.69 – 0.81 | 3.2 $\times 10^{-13}$ |
|          | Rs1768208 – 39498257 | MOBP               | 0.36    | 0.29    | 0.70   | 0.63 – 0.79 | 10 $\times 10^{-10}$ | 0.35 | 0.29 | 0.74 | 0.67 – 0.82 | 1.3 $\times 10^{-8}$ | 0.72 | 0.67 – 0.78 | 1.0 $\times 10^{-16}$ |
|          | Rs8070723 – 41436651 | MAPT               | 0.05    | 0.23    | 5.50   | 4.40 – 6.86 | 2.1 $\times 10^{-51}$ | 0.06 | 0.23 | 4.74 | 3.92 – 5.74 | 4.8 $\times 10^{-67}$ | 5.46 | 4.72 – 6.31 | 1.5 $\times 10^{-116}$ |
| 17q21.31 | Rs242557 – 41375823 | MAPT               | 0.53    | 0.35    | 0.48   | 0.43 – 0.53 | 2.2 $\times 10^{-37}$ | 0.50 | 0.36 | 0.54 | 0.48 – 0.59 | 5.0 $\times 10^{-15}$ | 0.51 | 0.47 – 0.55 | 4.2 $\times 10^{-70}$ |
|          | Rs242557/ Rs8070723 | MAPT               | ---     | ---     | 0.66   | 0.58 – 0.74 | 1.3 $\times 10^{-11}$ | --- | --- | 0.74 | 0.67 – 0.83 | 6.3 $\times 10^{-8}$ | 0.70 | 0.65 – 0.76 | 9.5 $\times 10^{-18}$ |

a MAF, minor allele frequency;
b OR based on major allele;
c rs242557 controlling for rs8070723;

Abbreviations and gene symbols: $P_1$, stage 1 $P$ value; $P_2$, stage 2 $P$ value; $P_J$, joint $P$ value; STX6, syntaxin 6; EIF2AK3, eukaryotic translation initiation factor 2-α kinase 3; MOBP, myelin-associated oligodendrocyte basic protein; MAPT, microtubule associated protein tau; a summary of the function of each gene listed is in Supplementary Table 9. Associations were determined using an additive genetic model. Exploratory analyses (results not shown) of PSP using dominant and recessive models did not produce new loci although some of the associations in 17q21.31 were also consistent with these non-additive models. These less parsimonious models did not fit the data significantly better than the additive model. By evaluating 5000 SNPs with the smallest $P$-values in more complicated models involving main effects and interactions, no noteworthy gene-gene interactions were uncovered. There were additional SNPs in the regions for the above loci that were significant or strongly suggestive for association; however, they were no longer significant after controlling the most significant SNP in the region (Supplementary Table 5). All loci significant in the joint analyses remained so after controlling for the MAPT inversion (Supplementary Table 10).