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

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Author Contributions Co-first authors G.U.H., N.M.M., D.W.D., and P.M.A.S. and senior authors U.M. and G.D.S., contributed equally to this project. G.U.H. and U.M. initiated this study and consortium, drafted the first grant and protocol, coordinated the European sample acquisition and preparation, contributed to data interpretation, and contributed to the preparation of the manuscript. N.M.M. conducted the analyses and contributed to the preparation of the manuscript. D.W.D. contributed to study design, data interpretation, and contributed to the preparation of the manuscript. P.M.A.S. contributed in the selection of controls for both phases of the experiment, data QC, data analysis and content curation for the replication phase custom array. L.S.W. participated in the initial association analysis, eSNP and pathway analysis, and functional annotation of SNPs in top genes. L.K. participated in genotype QC and analysis. R.R and R.DeSilva participated in study design, sample preparation and revising the manuscript for content. I.Litvan, D.E.R., J.C.V., P.H., Z.K.W., R.J.U., J.V., H.I.H., R.G.G., W.M., S.G., E.T., B.B., P.P., and the PSP Genetics Study Group (R.L.A., E.A., A.A., M.A., S.E.A., J.A., T.B., S.B., D.B., T.D.B., N.B., A.J.W.B., Y.B., A.B., H.B., M.C., W.Z.C., R.C., C.C., P.P.D., J.G.D., L.D.K., R.Duara, A.Durr, S.E., G.F., N.A.F., R.F., M.P.F., C.G., D.R.G., T.G., M.Gearing, E.T.G., B.G., N.R.G.R., M.Grossman, D.A.H., L.H., M.H., J.J., J.L.J., A.K., H.A.K., I.Leber, V.M.L., A.P.L., K.L., C.Mariani, E.M., L.A.M., C.A.M., N.M., B.L.M., B.M., J.C.M., H.R.M., C.Morris, S.S.O., W.H.O., D.O., A.P., R.P., G.P., S.P.B., W.P., A.Rabano, A.Rajput, S.G.R., G.R., S.R., J.D.R., O.A.R., M.N.R., G.S., W.W.S., K.Seppi, L.S.M., S.S., K.Srulijes, P.S.G., M.S., D.G.S., S.T., W.W.T., C.Trenkwalder, C.Troakes, J.Q.T., J.C.T., V.M.V., J.P.G.V., G.K.W., C.L.W., P.W., C.Z., and A.L.Z.) participated in characterization, preparation and contribution of samples from patients with PSP. L.B.C. coordinated project, sample acquisition and selection, and managed phenotypes. M.R.H. conducted eSNP and pathway analysis. A.Dillman performed mRNA expression experiments in human brain. M.P.V. and D.G.H. performed mRNA expression experiments in human brain, contributed to the design of eQTL experiments. J.R.G. performed computational and statistical analysis of the expression QTL data, contributed to the design of eQTL experiments. M.R.C. and A.B.S. were responsible for overall supervision, design and analysis of eQTL experiments. J.C.V., M.J.F., L.I.G., J.H., A.J.L., participated in study design, and data analysis discussions. C.E.Y. and T.R. participated in the initial design of experiments. B.D. supervised analyses and contributed to the writing of the manuscript. H.H. supervised genotyping and platform and sample selection, participated in analyses, and reviewed the manuscript. G.D.S. led the consortium, supervised study design, coordinated the United States sample acquisition and preparation, contributed to data interpretation, and wrote and coordinated assembly of the manuscript.

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Abstract

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}) 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, Aβ 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*[15].

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[16] to evaluate population substructure. Clinically diagnosed PSP[17] is reasonably concordant with autopsy results[18]. 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[19], 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[20]. 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[21]. 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 ($p = 8.71 \times 10^{-28}$ for multiple SNPs), but also with *ARL17A* ($P = 9.2 \times 10^{-22}$), *PLEKHM1* ($P = 1.0 \times 10^{-9}$), and *LRRC37A4* ($P = 2.2 \times 10^{-35}$)[12]. 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 tauoptahies, 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

= 1.28×10^{-5} for association with PSP. *TOMM40* is adjacent to *APOE* and rs2075650 tags the AD risk allele, e4, in *APOE*. The effect in PSP is opposite that seen in AD: e4 frequency is elevated in AD and diminished in PSP (for rs2075650, the estimated MAF in cases is 0.11 *versus* 0.15 in both our young and older controls; r^2 between rs2075650 and e4 is 0.33).

Our work suggests a number of intriguing insights into PSP. One comes from *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[30], AD[31], and PD[32]. In PSP, activated PERK is in neurons, oligodendrocytes, and astrocytes[30]. In AD, activated UPR components are found in pre-tangle neurons in a number of brain regions[31]. In PD, UPR activation occurs in neuromelanin containing dopaminergic neurons in the substantia nigra[32]. How the UPR contributes to PSP pathogenesis is unclear because the primary mis-folded protein in PSP, tau, is not a secreted protein and thus is not expected to traffic through the ER.

The PSP susceptibility gene *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[33]. Stx6 is localized to the *trans*-Golgi network and endosomal structures[34]. Since our work implicates ER-stress in PSP pathogenesis, genetic variation at *STX6* could influence movement of mis-folded proteins from the ER to lysosomes *via* the endosomal system.

MOBP ($P_J = 1 \times 10^{-16}$), like the myelin basic protein gene (*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[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 *EIK2AK3*. 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[36,37].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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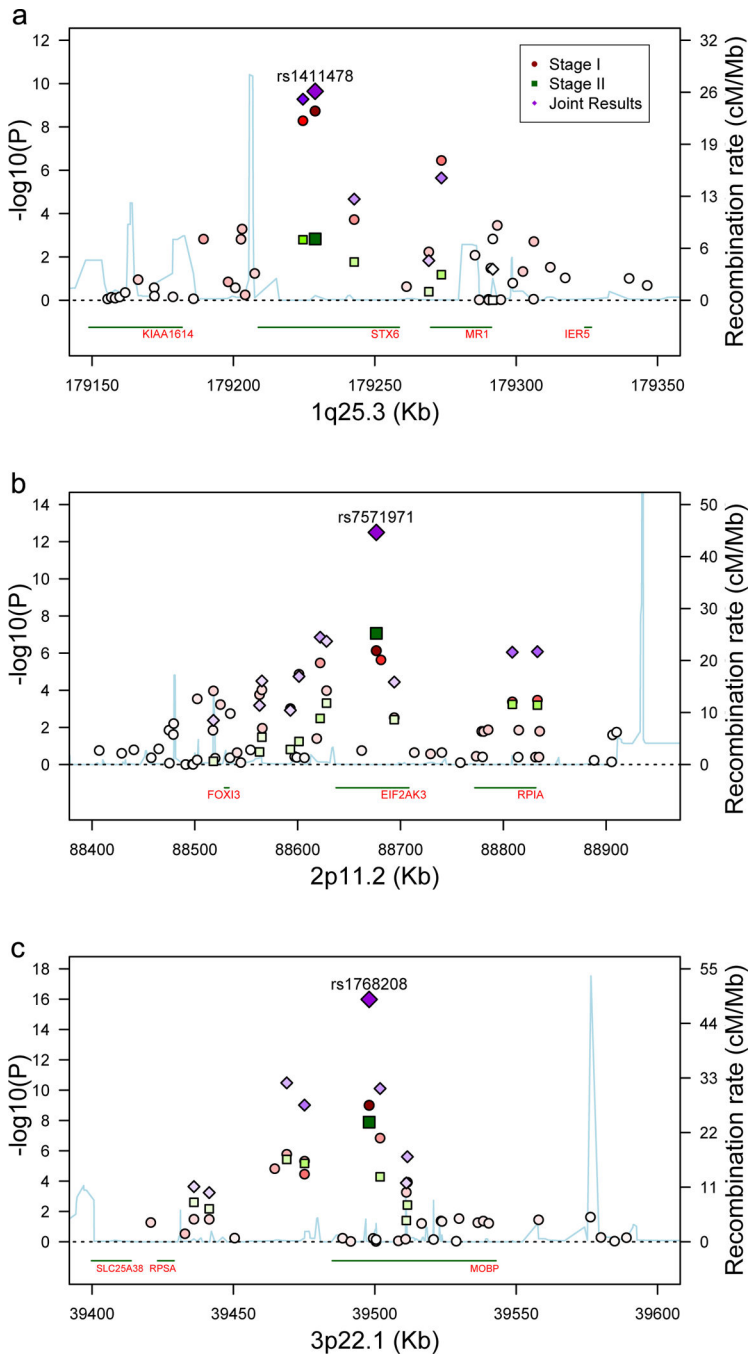

Figure 1.

(a) Association results for 1q25.3 *STX6*. (b) Association results for 2p11.2 *EIF2AK3*. (c) Association results for 3p22.1 *MOBP* regions. –log10 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.

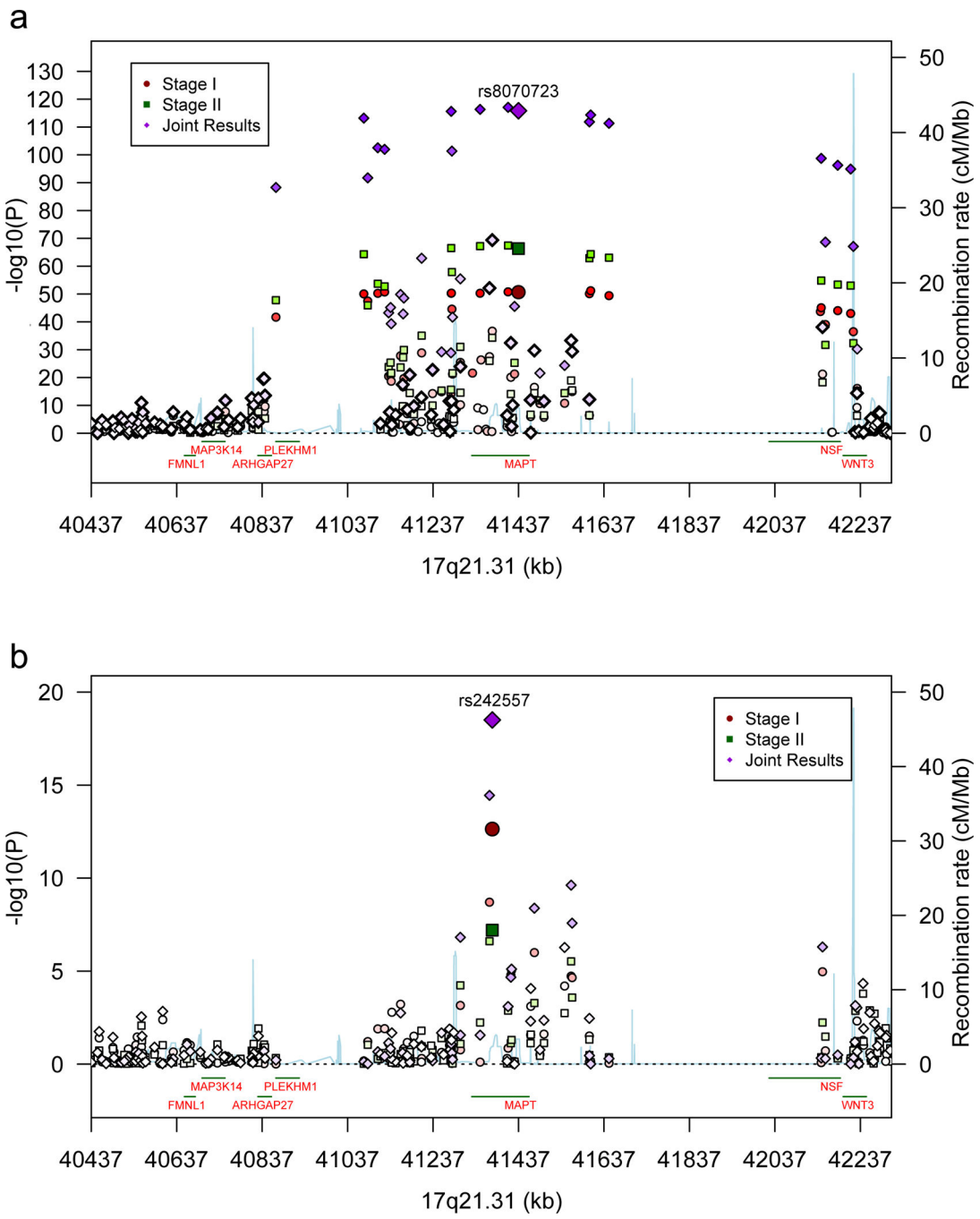

Figure 2.

(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.

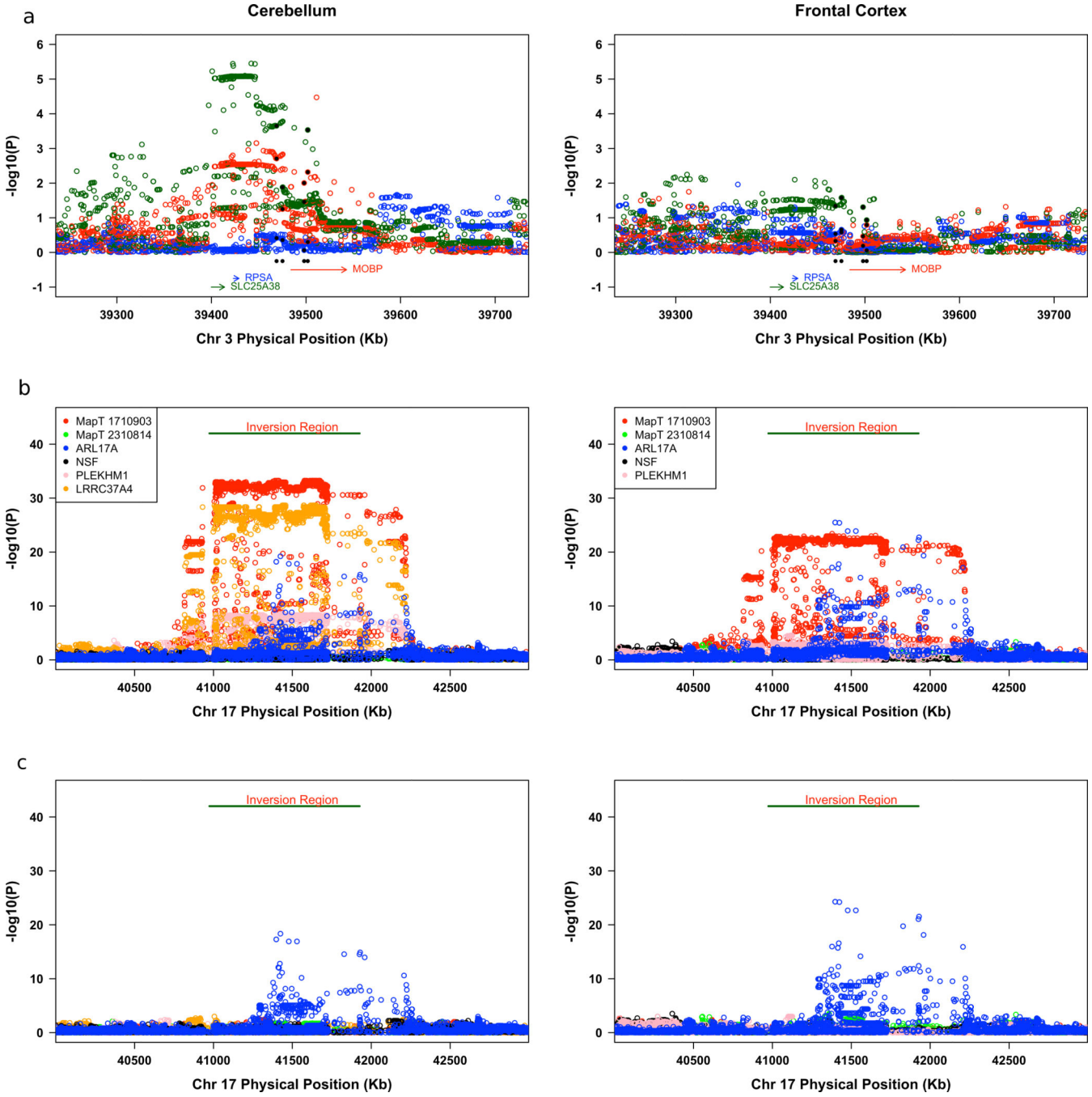

Figure 3.

(a) Association results for the relationship between SNP genotypes and mRNA transcripts from the cerebellum and frontal cortex for the *SLC25S38/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	n[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	
			MAF[a] Case	MAF Cont[b]	OR[c]/CI	P_1	MAF Case	MAF Cont	OR / CI	P_2	OR/CI	P_J
1q25.3	rs1411478 179,229,155	*STX6*	0.50	0.42	0.73 0.65 – 0.81	1.8×10^{-9}	0.46	0.43	0.85 0.77 – 0.94	1.5×10^{-3}	0.79 0.74 – 0.85	2.3×10^{-10}
2p11.2	rs7571971 88,676,716	*EIF2AK3*	0.31	0.26	0.75 0.66 – 0.84	7.4×10^{-7}	0.31	0.25	0.75 0.67 – 0.83	8.7×10^{-8}	0.75 0.69 – 0.81	3.2×10^{-13}
3p22.1	rs1768208 39,498,257	*MOBP*	0.36	0.29	0.70 0.63 – 0.79	10×10^{-10}	0.35	0.29	0.74 0.67 – 0.82	1.3×10^{-8}	0.72 0.67 – 0.78	1.0×10^{-16}
17q21.31	rs8070723 41,436,651	*MAPT*	0.05	0.23	5.50 4.40 – 6.86	2.1×10^{-51}	0.06	0.23	4.74 3.92 – 5.74	4.8×10^{-67}	5.46 4.72 – 6.31	1.5×10^{-116}
	rs242557 41,375,823	*MAPT*	0.53	0.35	0.48 0.43 – 0.53	2.2×10^{-37}	0.50	0.36	0.54 0.48 – 0.59	5.0×10^{-35}	0.51 0.47 – 0.55	4.2×10^{-70}
	[c]rs242557/ rs8070723	*MAPT*	---	---	0.66 0.58 – 0.74	1.3×10^{-11}	---	---	0.74 0.67 – 0.83	6.3×10^{-8}	0.70 0.65 – 0.76	9.5×10^{-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[38], 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).