Genetic determinants of survival in progressive supranuclear palsy: a genome-wide association study

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Summary

Background

The genetic basis of variation in the progression of primary tauopathies has not been determined. Here, we used a genome-wide association study (GWAS) to identify genetic determinants of survival in progressive supranuclear palsy (PSP).

Methods

Data were collected and analysed between 1st August 2016 and 1st February 2020. In stage one, we collected pathological and clinical-criteria diagnosed PSP cases from two separate cohorts (2011 PSP GWAS cohort cases from the Mayo Clinic and Munich brain banks; UCL PSP cohort cases from UK brain banks and the PROSPECT study). Cases were included if they had clinical data available on sex, age at motor symptom onset, disease duration (from motor symptom onset to death) and PSP phenotype (with reference to the 2017 Movement Disorder Society criteria). Genotype data from these cases were used to conduct a survival GWAS using a Cox-proportional hazards model. In stage two, replication data from additional Mayo Clinic brain bank cases, which were obtained after the 2011 PSP GWAS, were used for a pooled analysis. We assessed the eQTL profile of variants which passed genome-wide significance in our GWAS using the FUMA platform, and conducted colocalisation analyses using the eQTLGen and PsychENCODE datasets.

Findings

Data were available for 1,001 PSP cases of white European ancestry in stage one. We found a genome-wide significant association with survival at chromosome 12 (lead SNP: rs2242367 – $p=7.5x10^{-10}$; hazard ratio (95% confidence interval)=1.42 (1.22-1.67)). In stage two, the

addition of 238 cases resulted in significant pooled association statistics for rs2242367 (n=1,239; $p=1.3x10^{-10}$; hazard ratio (95% confidence interval)=1.37 (1.25-1.51). An eQTL database screen revealed that rs2242367 is associated with increased expression of *LRRK2* and long intergenic non-coding (lnc) RNAs, *LINC02555* and *AC079630.4*, in whole blood. Although we did not detect a colocalisation signal for *LRRK2*, analysis of the PSP survival signal and eQTLs for *LINC02555* in the eQTLGen blood dataset revealed a posterior probability of hypothesis 4 (PP4) of 0.77, suggesting colocalisation due to a single shared causal variant.

Interpretation

Genetic variation at the *LRRK2* locus was associated with survival in PSP. The mechanism of this association may be through a lncRNA-regulated effect on *LRRK2* expression as *LINC02555* has previously been shown to regulate *LRRK2* expression. *LRRK2* has been associated with sporadic and familial forms of Parkinson's disease, and our finding suggests a genetic overlap with PSP. Further functional studies will be important to assess the potential of *LRRK2* modulation as a disease-modifying therapy for PSP and related tauopathies.

Funding

PSP Association, CBD Solutions, Medical Research Council.

Introduction

Progressive supranuclear palsy (PSP) is a rapidly progressive neurodegenerative tauopathy. In the classical form, PSP-Richardson syndrome (PSP-RS), patients develop imbalance and frequent falls, bulbar failure and dementia, and have a mean survival of 6.9 years from symptom onset.[1] More recently defined PSP subtypes, such as PSP-Parkinsonism (PSP-P) and PSP-Progressive Gait Freezing (PSP-PGF), are associated with a slower rate of progression.[2] We have shown that the PSP phenotype is modified by variation at the *TRIM11/17* locus.[3] Additionally, certain clinical features, such as early dysphagia and cognitive symptoms, have been shown to predict a faster rate of progression.[4]

The pathology of PSP involves the deposition of insoluble hyperphosphorylated tau in neurons and astrocytes in sub-cortical and cortical brain regions. Recent work in animal models has shown that PSP-tau pathology is transmissible. Extracts from human PSP brain, inoculated into mouse brain, lead to PSP-type pathology in the recipient which replicates the morphology and immunohistochemical features of the human tauopathy.[5] Clinical disease progression relates to the sequential involvement of brain areas and systems. This may relate to different susceptibility and resistance of neurons, and cell to cell spread of pathology.[6]

Genome-wide studies in neurodegeneration have focused on case-control status, which have provided powerful insights into the aetiology of neurodegenerative disease. In PSP, common genetic variants have been associated with PSP risk.[7–9] However, therapeutic efforts focus on developing therapies which slow or halt disease progression, thus improving survival following a clinical diagnosis. Previous clinical trials targeting microtubule dysfunction and tau hyperphosphorylation have shown no benefit in slowing disease progression in PSP patients.[10,11] Current clinical trials in both PSP and Alzheimer's disease

(AD) patients aim to prevent cell to cell spread of tau by using neutralising antibodies against tau in the extracellular space.[12]

The genetic determinants of clinical disease progression and survival for neurodegenerative diseases are largely unexplored and are likely to provide important biological insights that may lead to new therapeutic approaches. A recent disease progression genome-wide association study (GWAS) in Huntington's disease identified a functional variant in *MSH3*, a DNA-repair gene, associated with disease progression based on longitudinal change in motor, cognitive and imaging measures.[13]

Here, we have conducted a GWAS using a Cox-proportional hazards model to identify genetic determinants of survival (from motor symptom onset to death) in PSP cases of white European ancestry.

Research in context

Evidence before this study: We searched PubMed for articles on progressive supranuclear palsy with no language restrictions from database inception up to July 1, 2020, using the following terms: "progressive supranuclear palsy AND genetics", "disease progression OR survival", focusing on studies that reported survival or clinical disease progression. No studies were found that had investigated the genetic determinants of PSP survival. However, of note, we have previously shown that PSP phenotype is associated with the rate of clinical disease progression and so we included phenotype as a covariate in our survival GWAS model.

Added value of this study: To our knowledge, this is the first survival GWAS of a primary tauopathy. Our study provides important evidence for the role of the *LRRK2* locus in modifying survival in PSP, and this association appears to be independent of the *LRRK2* risk signal previously associated with Parkinson's disease. The results of our eQTL database screen and colocalisation analyses highlight the potential interaction between non-coding RNA and gene expression, and the impact of this on the progression of neurodegenerative diseases.

Implications of all the evidence available: Our study provides evidence for an overlap in the genetic aetiology of PSP and Parkinson's disease. These findings pave the way for further functional studies on the impact of LRRK2 on tau pathology. LRRK2 modulation is currently being trialled as a disease-modifying therapy in Parkinson's disease patients, and our study highlights the potential of this approach having a therapeutic role in tauopathies. In the meantime, further genetic replication of this finding may provide

evidence for using *LRRK2* locus genotype for predicting progression in clinical practice, and the stratification of PSP patients for future clinical trials.

Methods

Study design and participants

Data were collected and analysed between 1st August 2016 and 1st February 2020. In stage one, cases with either a neuropathological or clinical diagnosis of PSP were identified from two separate cohorts: 2011 PSP GWAS cohort cases from the Mayo Clinic and Munich brain banks (pathologically diagnosed); UCL PSP cohort cases from UK brain banks (pathologically diagnosed) and the Progressive Supranuclear Palsy-Cortico-Basal Syndrome-Multiple System Atrophy (PROSPECT) study (clinically diagnosed) (Supplementary Table 1, p. 2). Local ethics committees at each of the brain banks approved this work and each patient had previously provided written informed consent for their clinical data and DNA to be used in research projects, including genetic studies. The UCL PSP cohort included clinically diagnosed cases from the PROSPECT study, a UK-wide longitudinal study of patients with atypical parkinsonian syndromes.[2] These patients had provided written informed consent for their clinical data and DNA to be used in research projects, including genetic studies. A subset of deceased PROSPECT study PSP cases had provided separate written informed consent for post-mortem neuropathological confirmation of diagnosis at Queen Square (diagnosis by Z.J., J.L.H. and T.R.) and Cambridge (diagnosis by K.S.J.A.) brain banks.

In stage two, cases with a neuropathological diagnosis of PSP (diagnosis by D.W.D) were identified from the Mayo Clinic brain bank. Of note, these additional cases had entered the brain bank after publication of the 2011 PSP case-control GWAS,[7] and had provided written

informed consent for their clinical data and DNA to be used in research projects, including genetic studies.

In both stage one and two, all PSP cases were considered for inclusion in this study, provided they had an adequate depth of phenotype data available for clinical characterisation, and passed genotype quality control steps (see below).

Procedures

In stage one and two, all PSP cases were assigned a Movement Disorder Society (MDS) PSP diagnostic criteria phenotype based on clinical features that were present in the first three years from motor symptom onset, using consensus criteria on application of the diagnostic criteria.[14,15] Cases were subsequently stratified into PSP-RS and non-PSP-RS groups, where non-PSP-RS consisted of PSP-parkinsonism and PSP-progressive gait freezing phenotypes. For pathologically diagnosed brain bank cases, this approach was applied retrospectively using detailed case notes (stage one cases by E.J., D.W.D., G.R. and G.U.H.; stage two cases by S.K. and D.W.D.). For clinically diagnosed PROSPECT study cases included in stage one, patients were assigned a baseline PSP phenotype on entry to the study by E.J. using the same criteria as above. Of note, all included PROSPECT study PSP cases were at least three years into their disease course (from motor symptom onset) and fulfilled at least "possible" diagnostic criteria for a PSP phenotype.

In addition, the following clinical data was collected for cases in stage one and two: sex; age at motor symptom onset; disease duration from motor symptom onset to death, or motor symptom onset to date of censoring (01/12/2019) for living PROSPECT study PSP cases. Motor symptom onset was defined as the point at which motor dysfunction was persistent

and affected normal activities of daily living. Cases were excluded from the study if there was inadequate clinical data to accurately assign both PSP phenotype and disease duration. In stage one, cases underwent genotyping using the Illumina NeuroChip (UCL cohort cases) or the Illumina Human 660W-Quad Infinium chip (2011 GWAS cohort cases).[7,16] The two datasets were then merged and imputed as one common dataset. In stage two, lead SNPs of all genome-wide significant loci from the stage one GWAS were genotyped using a TaqMan assay. A detailed description of the genotype data and imputation methods used can be found in the Supplementary Material, pp. 3-4.

As most GWAS loci are thought to operate by regulating gene expression,[17,18] we screened all significant SNPs from our GWAS for expression quantitative trait loci (eQTL) signals using Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA) (https://fuma.ctglab.nl).[19] SNPs were defined as eQTLs if their false discovery rate (FDR) corrected p-value was significant ($p<0.05$). A detailed description of FUMA's eQTL data sources are available at https://fuma.ctglab.nl/tutorial#snp2gene. Additionally, the North American Brain Expression Consortium (NABEC) eQTL dataset (213 human frontal cortex samples) was analysed (dbGaP Study Accession: phs001300.v1.p1).

We applied coloc[20] (version 3.2.1) to evaluate the probability of colocalisation between two traits, which in this case were PSP survival and regulation of gene expression via eQTLs. We used *cis*-eQTLs from eQTLGen[21] and PsychENCODE[22] datasets, which represent the largest human blood and brain expression datasets, respectively (eQTLGen, sample size = 31,684 individuals; PsychENCODE, sample size = 1,387 individuals). Loci with a posterior probability of H_4 (PP4) ≥ 0.75 were considered colocalised due to a single shared causal variant. A detailed description of the methods used can be found in the Supplementary Material, p. 4.

A subset (n=140) of PROSPECT study PSP cases of white European ancestry underwent whole-genome sequencing (WGS) at Uniformed Services University of Health Sciences (Bethesda, MD, USA). These samples represent all of the PROSPECT study PSP cases that we had recruited as of 01/12/2017 when samples were sent for WGS. A detailed description of the methods used can be found in the Supplementary Material, pp. 4-5.

Statistical analysis

In stage one we began by assessing the association between known PSP genetic risk and phenotype variants[3,7–9] and survival using a Cox-proportional hazards model that adjusted for sex, age at motor symptom onset and the first three genetic principal components (PCs) derived from PCA. We then conducted a survival GWAS using the same model, with the addition of PSP phenotype (PSP-RS or non-PSP-RS) as a covariate based on the results of the initial analysis. Of note, the model was applied to each SNP in our dataset one at a time, resulting in each SNP having a hazard ratio, 95% confidence interval and associated p-value. The GWAS was repeated for only pathologically diagnosed cases to assess for differences in association statistics, which may be due to the inclusion of clinically diagnosed cases that were incorrectly diagnosed with PSP in the original stage one GWAS. We used Akaike Information Criterion (AIC) analyses[23] to consider the use of additional covariates (study site and further genetic PCs) by assessing the goodness of fit of the model with and without each variable. All reported significant SNPs had a Cox.zph p-value >0.05, indicating that the model adhered to the assumption of proportional hazards. Code for the Cox-proportional hazards survival model are available on GitHub (https://github.com/huw-morris-lab/PSP-survival-gwas). These analyses (using the 'survival' and 'survminer' packages) and the

creation of Figure 1a, 2 and 3 were conducted in R (version 3.3.2). Figure 1b was created using LocusZoom (version 0.10). The Bonferroni-corrected threshold for genome-wide significance in stage one was set at $p<1.0x10^{-8}$. To assess for the presence of more than one independent signal within a genome-wide significant locus, we re-ran the stage one GWAS as a conditional analysis, with the lead SNP genotype included as a covariate in the model. For additional cases in stage two, the same Cox-proportional hazards survival model was applied to genotype results of the lead SNP from the stage one GWAS, with significance set at $p<0.05$. The genotype results of this SNP for stage one and stage two cases were then pooled and analysed to obtain a more accurate estimate of the effect size of the lead SNP, accounting for all of the cases included in this study.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 1,033 cases were considered for inclusion in stage one. Following post-imputation data quality control, 4,817,946 common (minor allele frequency ≥1%) SNPs were used for analyses. 32 cases were excluded due to either insufficient clinical data or failing genotype data quality control, including one case that was found to have a previously described *MAPT* L284R mutation.[24] This left 1,001 PSP cases of white European ancestry (confirmed by genetic PCA) for analyses, derived from two cohorts, with pathological confirmation of PSP achieved in 100% of deceased cases that had undergone post-mortem examination (n=841)

(Supplementary Table 1, p. 2). 895/1001 (89.4%) of our whole cohort were deceased at the date of censoring (Table 1).

Table 1: Clinical characteristics of stage one PSP survival GWAS cases and stage two replication cases

	Stage one						Stage two	
	Whole cohort		UCL cohort		2011 GWAS cohort			
	PSP-RS	non-PSP-RS	PSP-RS	non-PSP-RS	PSP-RS	non-PSP-RS	PSP-RS	non-PSP-RS
No. of subjects	720	281	395	182	325	99	220	18
% male subjects	59.2	51.2	62.3	51.1	55.4	51.5	52.7	55.6
Mean age at motor symptom onset, years [SD]	67.83 [7.48]	66.79 [8.38]	68.14 [7.08]	66.69 [8.10]	67.45 [7.92]	66.97 [8.90]	67.56 [8.15]	67.67 [6.21]
No. of cases deceased at the date of censoring*, (%)	652/720 (90.6)	243/281 (86.5)	327/395 (82.8)	144/182 (79.1)	325/325 (100)	99/99 (100)	220/200 (100)	18/18 (100)
Mean disease duration in deceased cases, years [SD]	6.38 [2.10]	9.81 [3.50]	6.06 [1.86]	9.35 [3.22]	6.69 [2.27]	10.48 [3.79]	6.22 [2.27]	9.67 [3.51]

PSP-RS = PSP-Richardson syndrome, non-PSP-RS = Combined PSP-parkinsonism and PSP-progressive gait freezing cases. SD = standard deviation (SD). ***** = Date of censoring was 01/12/2019.

Using a Cox-proportional hazards survival model, we found no association between survival and all of the known PSP risk variants ($p>0.05$) after adjusting for sex, age at motor symptom onset and the first three genetic PCs to account for population substructure (Supplementary Table 2, p. 6). There was an association between the known PSP phenotype *TRIM11/17* locus (rs564309) and survival – $p = 0.02$, hazard ratio (95% confidence interval) =

0.88 (0.80-0.97), but this signal was attenuated when phenotype was added in as a binary (PSP-RS or non-PSP-RS) covariate. We then conducted a survival GWAS using sex, age at motor symptom onset, PSP phenotype and the first three genetic PCs as covariates. The genomic inflation factor (lambda) was 1.05, suggesting that there was no confounding by population stratification. In the whole-cohort analysis we found a genome-wide significant association signal at chromosome 12 (Figure 1a), with eight SNPs reaching the significance threshold. The lead SNP at this locus, rs2242367 (GRCh37 chr12:40413698), was associated with PSP survival – $p = 7.5x10^{-10}$, hazard ratio (95% confidence interval) = 1.42 (1.22-1.67) (Figure 1b), with the minor allele associated with worsening survival – Kaplan-Meier survival analysis log-rank test $p = 5.5x10^{-4}$ (Figure 2). A summary of sub-genome-wide significant signals can be found in Supplementary Table 3, pp. 7-9. The association between rs2242367 and survival was observed in each separate cohort (Table 2). A conditional analysis that adjusted for rs2242367 genotype did not reveal other independent association signals. We referred to the summary statistics of previous GWAS and found that rs2242367 was not associated with PSP risk or PSP phenotype (Supplementary Table 4, p. 10). Our AIC analyses justified the approach of not adjusting for study site and using only the first three PCs as covariates to avoid overfitting (Supplementary Material, p. 10). To ensure that our genetic signal was not being driven by non-PSP patients in our small subset of clinically diagnosed cases, we repeated the stage one analysis using only pathologically diagnosed PSP cases (n=841). Reassuringly, this resulted in rs2242367 remaining as our lead SNP with similar association statistics ($p = 6.9x10^{-8}$, hazard ratio (95% confidence interval) = 1.37 (1.22-1.54)) in comparison to the original analysis, with no new genome-wide significant SNPs identified.

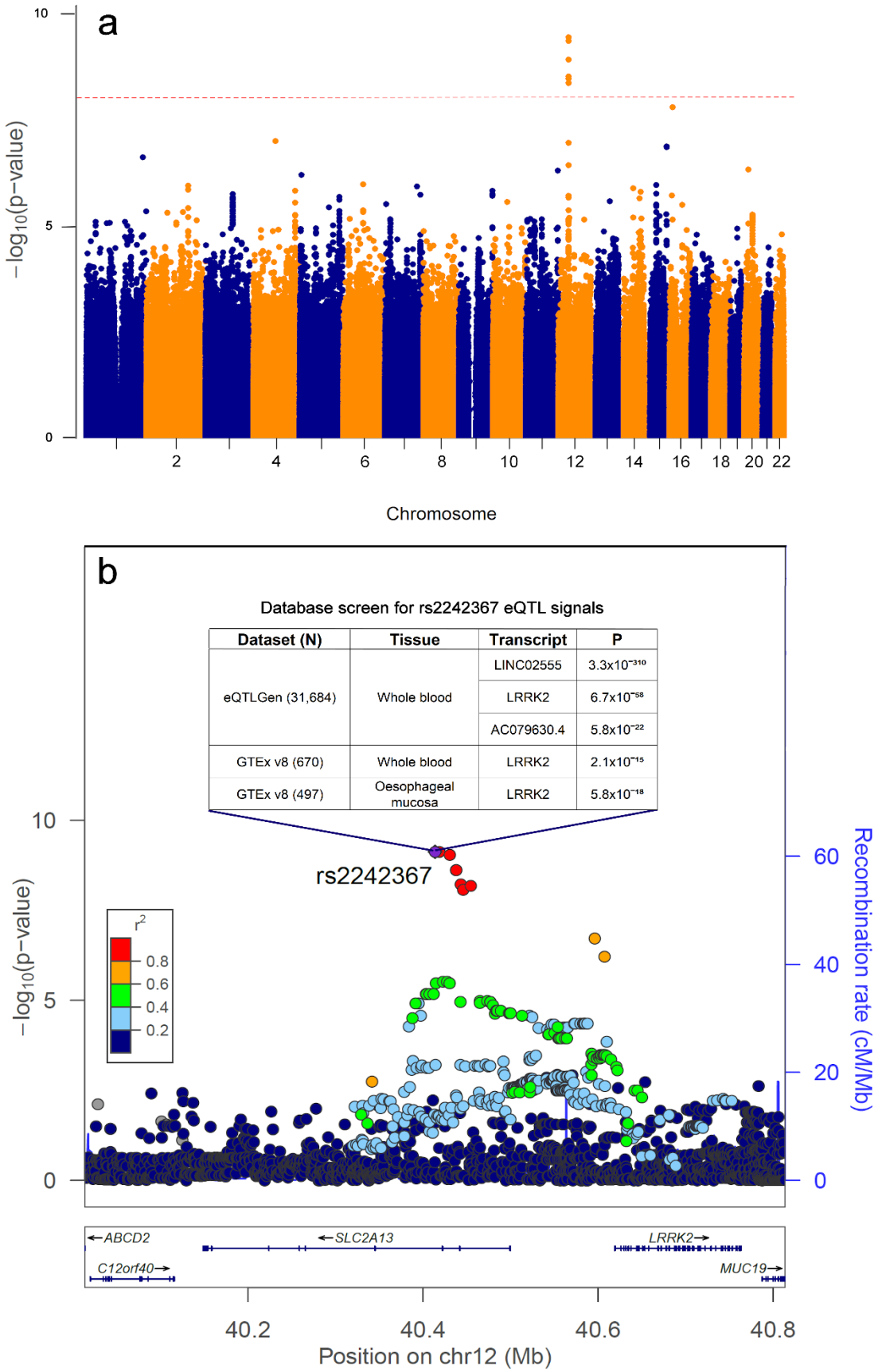

Figure 1: Manhattan and regional association plots, with supporting eQTL data, highlighting *LRRK2* association with PSP survival

a, Manhattan plot of PSP survival GWAS, highlighting a genome-wide significant signal at chromosome 12. The red line indicates the Bonferroni-corrected threshold for genome-wide significance ($p<1.0x10^{-8}$). b, Regional association plot of PSP survival GWAS, identifying rs2242367 as the lead SNP with associated significant results from an eQTL database screen. $r^2 = r^2$ linkage disequilibrium. SNP positions, recombination rates and gene boundaries are based on GRCh37/hg19.

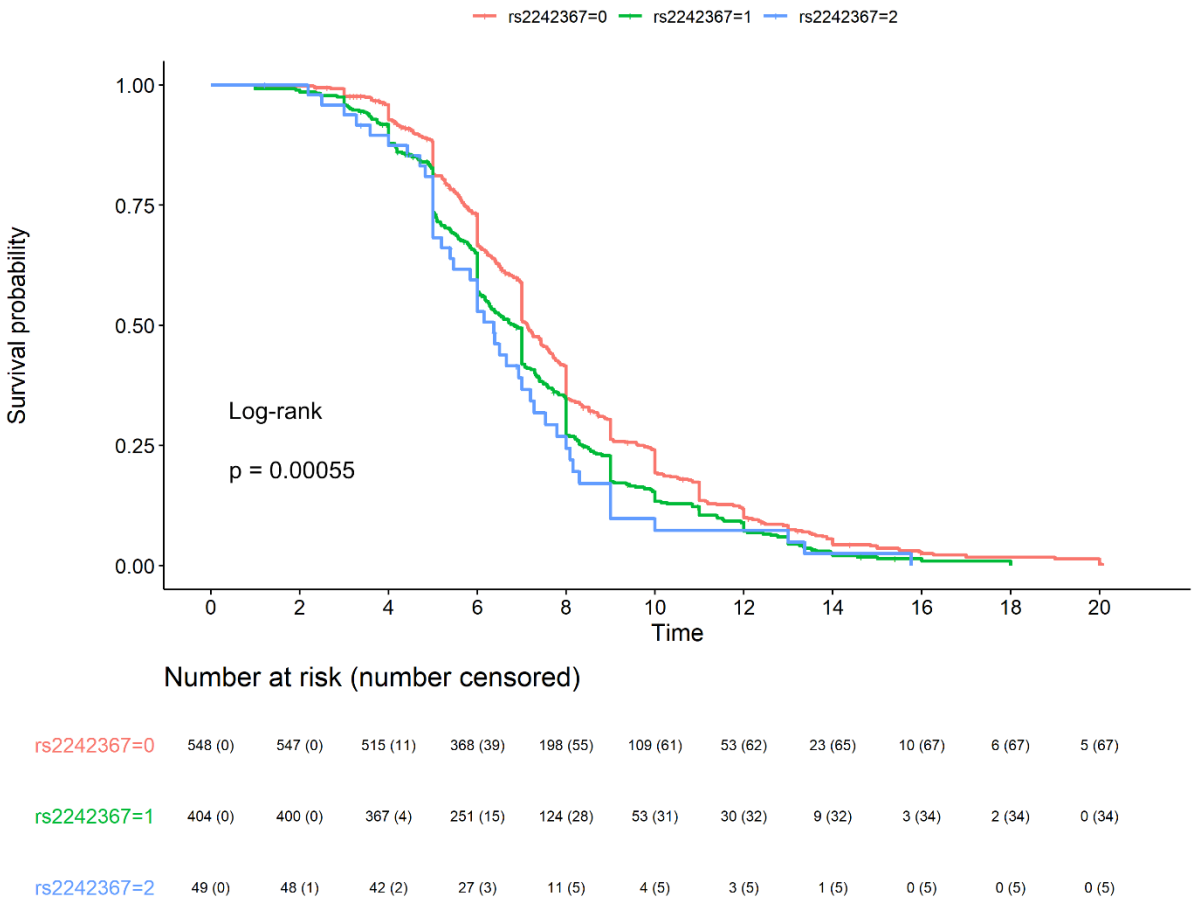

Figure 2: Kaplan-Meier survival curve for rs2242367

Kaplan-Meier survival curve highlighting differences in survival in PSP, comparing cases carrying rs2242367 GG genotype, '0' risk allele (red line) AG genotype, '1' risk allele (green line) and AA genotype, '2' risk alleles (blue line). Analysis of rs2242367 under an additive model showed that carrying an A allele was significantly associated with decreased survival (log-rank test $p = 5.5x10^{-4}$).

In stage two, an additional 415 pathologically diagnosed PSP cases of white European ancestry from the Mayo Clinic brain bank were genotyped for rs2242367 using a TaqMan assay. 238/415 (57%) of these cases had adequate phenotype data to accurately assign a

PSP phenotype and disease duration using the same methods as in stage one and were therefore analysed (Table 1). No evidence of deviation from the Hardy-Weinberg equilibrium was observed. Using the same Cox-proportional hazards survival model as in stage one, we found that rs2242367 was associated with PSP survival – p = 0.049, hazard ratio (95% confidence interval) 1.22 (1.00-1.48). There appeared to be an additive allele / survival relationship in deceased cases across all three cohorts, and in both PSP-RS and non-PSP-RS cases (Table 2).

A pooled Cox-proportional hazards survival analysis of rs2242367 genotype using all stage one and stage two cases (n=1,239) was significant – p = 1.3×10^{-10}, hazard ratio (95% confidence interval) 1.37 (1.25-1.51).

Table 2: rs2242367 association statistics and impact of genotype on disease duration in deceased PSP cases

	Stage one				Stage two		Pooled analysis	
	UCL cohort		2011 GWAS cohort					
	PSP-RS	non-PSP-RS	PSP-RS	non-PSP-RS	PSP-RS	non-PSP-RS	PSP-RS	non-PSP-RS
No. of subjects	395	182	325	99	220	18	940	299
Mean disease duration in deceased cases with rs2242367 GG genotype, years [SD]	6.35 [1.93]	10.15 [3.07]	7.07 [2.39]	11.14 [4.16]	6.47 [2.31]	10.55 [3.75]	6.64 [2.23]	10.56 [3.59]
Mean disease duration in deceased cases with rs2242367 AG genotype, years [SD]	5.73 [1.73]	8.72 [3.08]	6.24 [2.07]	9.85 [3.26]	5.88 [2.25]	9.00 [2.92]	5.97 [2.00]	9.19 [3.17]
Mean disease duration in deceased cases with rs2242367 AA genotype, years [SD]	5.47 [1.44]	7.86 [3.89]	6.29 [1.86]	9.33 [4.04]	5.89 [1.81]	6.50 [2.12]	5.86 [1.71]	7.96 [3.64]
rs2242367 risk allele frequency*, %	23.5	28.0	24.9	26.3	25.2	25.0	24.4	27.3
rs2242367 hazard ratio (95% CI)	1.46 (1.25-1.71)		1.39 (1.19-1.63)		1.22 (1.00-1.48)		1.37 (1.25-1.51)	
rs2242367 p-value	$1.4x10^{-6}$		$6.7x10^{-5}$		0.049		$1.3x10^{-10}$	

rs2242367 major allele = G, rs2242367 minor allele = A, SD = standard deviation, 95% CI = 95% confidence interval, PSP-RS = PSP-Richardson syndrome, non-PSP-RS = Combined PSP-parkinsonism and PSP-progressive gait freezing cases. ***** = rs2242367 risk allele frequency in 7,692 reference controls of non-Finnish white European ancestry was 28.2%, taken from https://gnomad.broadinstitute.org on 10/01/2020.

There are no coding variants in linkage disequilibrium (LD) with the lead SNP rs2242367 as defined by the region encompassed by variants with an $r^2>0.3$ (Supplementary Figure 1, p. 14). We mined available eQTL datasets to better understand the molecular mechanisms

underlying PSP survival. Using FUMA, we found that rs2242367, and associated SNPs in high r^2 LD (>0.80), were significant eQTLs for *LRRK2* expression in whole blood and oesophagus in the eQTLGen and GTEXv8 datasets respectively (Figure 1b). rs2242367 was also an eQTL for the long intergenic non-coding (lnc) RNAs, *LINC02555* (ENSG00000260943, $p=3.3x10^{-310}$) and *AC079630.4* (ENSG00000223914, $p=5.8x10^{-22}$), in the eQTLGen whole blood dataset. Of note, the minor allele at rs2242367, which we show to be associated with reduced survival in PSP, was associated with increased expression of *LRRK2*, *LINC02555* and *AC079630.4*. Although FUMA's eQTL database screen did not highlight any significant eQTL signals in brain, we did note that rs2242367 and its surrounding significant SNPs reached nominal significance ($2.1x10^{-5}$ – $9.1x10^{-5}$) in GTEx version 8 for impacting on the expression of *LRRK2* in the caudate, and *AC079630.4* in the pituitary. Additionally, we interrogated the NABEC brain dataset and found no significant eQTL signals associated with rs2242367.

Given the findings from the eQTL database screen, we performed colocalisation analyses to evaluate the probability that the same causal SNP was responsible for modifying PSP survival and modulating gene expression. eQTLs were obtained from eQTLGen and PsychENCODE, the largest available human blood and brain eQTL datasets, respectively. Our analyses found no colocalisation signals between PSP survival and *LRRK2* expression. However, we identified a colocalisation of signals (PP4 = 0.77) between PSP survival loci and blood-derived eQTLs regulating the expression of the lncRNA, *LINC02555* (Figure 3) (Supplementary Table 5, pp. 11-12). No significant associations between PSP survival loci and eQTLs from PsychENCODE were found (Supplementary Table 5, pp. 11-12).

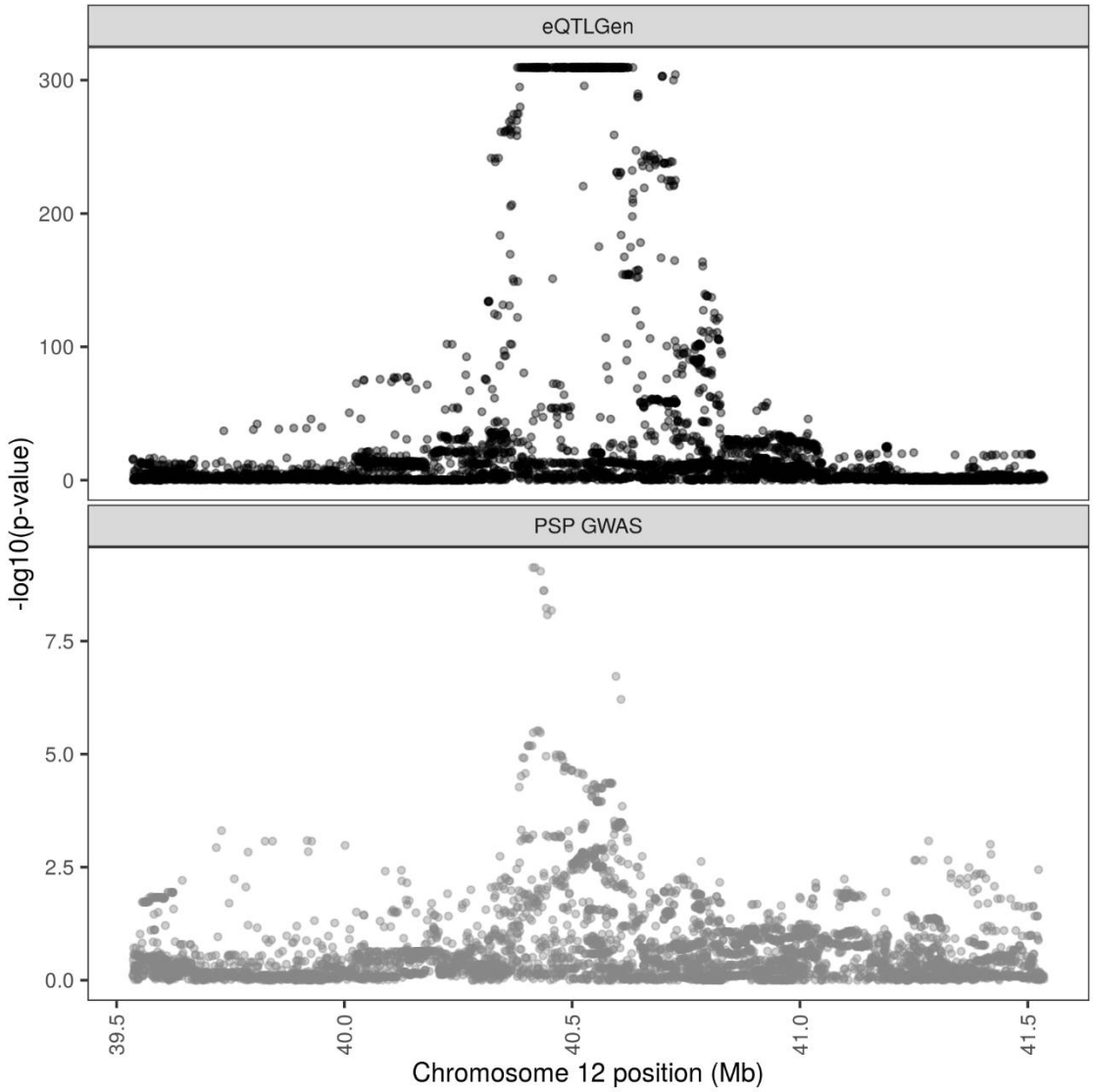

Figure 3: Colocalisation of blood-derived eQTLs regulating *LINC02555* expression and overlapping PSP survival loci

Plot of -$\log_{10}$(p-values) for the region surrounding *LINC02555* shows colocalisation of blood-derived *LINC02555* eQTLs (top panel) and PSP survival signal (bottom panel) (PP4 = 0.77). In the top panel: black dots = eQTL p-values; grey dots = PSP survival p-values. The black bar in the top panel represents a large density of eQTLs with the same p-value.

A subset of the UCL cohort cases (n=140) underwent WGS. In these cases, the genotypes of our eight genome-wide significant SNPs (rs2242367, rs1542594, rs2128276, rs11174918, rs10878029, rs7967822, rs11564279 and rs1871895) had 100% concordance between WGS and chip-based imputed datasets. We applied the Cox-proportional hazards survival model on WGS variants with a minor allele frequency ≥0.1% in our region of interest (GRCh38 chr12:39225001-41369277) and identified 214 variants with a stronger association signal than rs2242367 ($p<0.01$). All of these were non-coding variants in LD with rs2242367 (r^2=0.30-0.35, D'=0.96-1.0) and were eQTLs ($p<1.0x10^{-20}$) for increasing *LRRK2*, *LINC02555* and *AC079630.4* expression in whole blood in the eQTLGen dataset. None of the variants were significant eQTLs for *LRRK2*, *LINC02555* or *AC079630.4* expression in brain (FDR-corrected $p>0.05$).

Discussion

We have shown that variation at the *LRRK2* locus is a genetic determinant of survival in the primary tauopathy, PSP. This signal was shown in each of our cohorts (total n = 1,239), suggesting that the finding is robust. A particular strength of this study was the fact that our outcome measure was disease duration that captures the entire clinical disease course, from motor symptom onset to death. This is in contrast to other neurodegenerative disease progression GWAS that have used longitudinal rate of change in clinical rating scale scores,[13,25] which only capture specific time points in the disease course, and are subject to inter- and intra-rater variability. Diagnostic accuracy was not a limitation in this study as the majority of cases we included had pathological confirmation of PSP pathology at post-mortem. Previously we have shown that a clinical diagnosis of PSP using the MDS diagnostic criteria is strongly predictive of underlying PSP pathology.[2] Nevertheless, our sub-analysis of

only pathological cases further supports our findings, and does not suggest that there was significant inclusion of clinically diagnosed non-PSP cases in the whole-cohort analysis. Assignment of motor symptom onset in our study was made blinded to the genotype results using a standard definition.

LRRK2 is an established major risk factor for Parkinson's disease (PD) with common and rare (G2019S) variants associated with disease.[26] The lead SNP from our PSP survival GWAS, rs2242367, lies within intron 3 of *SLC2A13,* 190Kb from the common *LRRK2* risk SNP for PD, rs76904798,[26] which has also been nominally associated ($p=3.0x10^{-4}$) with the rate of motor progression of PD.[25] The two variants are in low r^2 LD in non-Finnish white European populations, but with a high D' ($r^2=0.05$, D'=0.90) (LDlink v3.8). Of note, rs2242367 had association statistics that approached genome-wide significance in the most recent PD case-control GWAS ($p = 1.6x10^{-7}$, odds ratio (95% confidence interval) = 0.94 (0.92-0.96)).[26] The allele frequency of rs2242367 is 28% while the allele frequency of rs76904798 is 13% (GnomAD v2.1.1), and so the *LRRK2* PD risk SNP may define a sub-haplotype of the ancestral PSP survival haplotype. This region also contains association signals for two immune/inflammatory diseases, Crohn's disease[27] and leprosy.[28] None of the risk SNPs at this locus identified through case-control GWAS for PD, Crohn's disease and leprosy had significant association statistics in the PSP survival GWAS (Supplementary Table 6, p. 13). Our analyses suggest that the genetic signal at the *LRRK2* locus associated with PSP survival is distinct from the *LRRK2* locus signals identified in the PD case-control GWAS, although the high D' LD statistics between rs2242367 and 76904798 mean that we cannot rule out the possibility that the two signals are related. However, a conditional analysis on our lead SNP did not identify any independent association signals. A formal genetic correlation analysis of

the PSP survival and PD risk GWAS results will help to explore the potential genetic overlap between these traits. Additionally, analysis of our subset of cases that had WGS data available suggests that the association signal at rs2242367 may be part of a haplotype block, paving the way for better-powered studies using WGS datasets to clarify this.

LRRK2 is expressed in multiple human tissues including brain and whole blood. In brain, it is expressed ubiquitously across all regions and is found in neurons, astrocytes, microglia and oligodendroglia.[29] Pathogenic mutations in *LRRK2* lead to phosphorylation of a subset of Rab proteins which have important roles in the formation and trafficking of intracellular vesicles.[30] This in turn may affect proteostasis and the inflammatory response, both of which may be important in mediating disease progression in PSP.[31]

There is also an established link between *LRRK2* and tau pathology, which was reported in chromosome 12 linked PD families before the identification of the *LRRK2* gene.[32] In rare cases, *LRRK2* mutations have been identified in patients with PSP-tau pathology at post-mortem.[33] The link between *LRRK2* and tau pathology has previously been explored in cell and animal models, identifying dysregulation of actin and mitochondrial dynamics, and the impairment of tau degradation via the proteasome.[34–36] Most recently, a whole-genome CRISPR screen has provided functional support for our genetic findings by identifying LRRK2-regulated endocytosis as a major mechanism for extracellular tau uptake by human neurons.[37]

In our eQTL database screen, the lead SNP, rs2242367, was shown to be an eQTL for regulating *LRRK2* expression in whole blood. Of note, when referring to the two brain-

derived regulatory tracks (University of California, San Francisco brain DNA methylation; University of Massachusetts Medical School brain histone) in the University of California, Santa Cruz genome browser (https://genome.ucsc.edu/), we found that rs2242367 lies in a region that is methylated and may therefore impact on the regulation of gene expression. However, our colocalisation analyses using the largest brain and blood-derived eQTL datasets demonstrated that *LRRK2* eQTLs and our PSP survival signal do not colocalise, but rather represent two independent causal variants (PP3 > 0.99 in both eQTL datasets). Instead, we identified a colocalisation signal for the lncRNA, *LINC02555*, which is <500Kb proximal to *LRRK2*. In GTEx version 8, *LINC02555* was shown to have low levels of expression in bulk RNA analysis from brain (https://www.gtexportal.org/home/gene/ENSG00000260943). However, lncRNAs are known to be less expressed than mRNAs with highly variable cell-specific expression[38] and so may be hard to detect through bulk RNA sequencing. Nevertheless, it is well established that some lncRNAs control the expression of *LRRK2*,[39] and silencing of *LINC02555* in papillary thyroid carcinoma cells has been shown to decrease *LRRK2* expression and enhance autophagy in association with reduced tumour formation.[40] Therefore, lncRNAs may be important in regulating state-specific, regional or cell-type-specific gene expression. The strongest evidence for the effect on expression is reported from blood rather than bulk RNA analysis from brain. This may relate to the cell types present and sample size differences in blood and brain expression datasets. In the PsychENCODE bulk RNA dataset, most of the power for detecting eQTL signals in the brain comes from astrocytes and neurons, with microglia representing only 5% of normalised cell fractions.[22]

Alternatively, the predominant effect on expression in blood may relate to peripheral immune response-driven neuroinflammation or be due to a specific effect in monocyte/microglial lineage cells.[41] Increased *LRRK2* expression may result in a reactive microglia-induced pro-inflammatory state which drives ongoing accumulation of misfolded tau protein and clinical disease progression.[42,43] This hypothesis is supported by *in vivo* positron emission tomography evidence of a pattern of microglial activation which correlates with disease severity in PSP,[44,45] and co-localises with the tauopathy of PSP and other forms of frontotemporal lobar degeneration tauopathy.[46] In mouse models, microglial inflammatory responses are attenuated by LRRK2 inhibition[43] and this strategy is currently under investigation in PD as a disease-modifying therapy (https://clinicaltrials.gov/ct2/show/NCT03710707?term=dnl201&draw=1&rank=1).

We acknowledge potential limitations of the study. Firstly, our stage one and stage two cohorts were not independent as they included cases recruited at the same centre. Secondly, our approach of merging different chip-based genetic datasets prior to imputation will reduce, albeit to a small extent, the total number of SNPs available for analysis post-imputation,[47] with the Illumina NeuroChip having less dense genome coverage in comparison to the Illumina Human 660W-Quad Infinium chip. While this does not invalidate our primary findings, it may have led to us missing out on the identification of other signals. We believe that future large-scale analyses of WGS data is the most effective way of replicating our findings, and discovering other loci associated with PSP survival. Thirdly, as we have shown, bulk RNA analysis in brain is relatively underpowered to detect eQTL signals. In addition, we are limited in our ability to detect cell-specific effects on gene expression. The advent of expression analysis in defined brain cell subpopulations will help to clarify the functional consequences of genetic variation which modulates survival in PSP.

Future studies on the *LRRK2* locus as a potential genetic determinant of disease progression and survival in related tauopathies, namely AD, frontotemporal degeneration and corticobasal degeneration, are of great importance. Additionally, our study paves the way for further functional work assessing the impact of *LRRK2* on tau aggregation, and exploration of LRRK2 inhibition as a therapeutic approach in patients with tauopathies.

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Author contributions

E.J. and H.R.M. designed the study. E.J. wrote the manuscript. E.J. and M.S. did the statistical analysis and created the figures. All authors were involved in data collection and interpretation, and drafting of the manuscript. All authors critically reviewed the manuscript and approved the final version.

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