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Association of *TRIM11* rs564309 with tau pathology in Progressive Supranuclear Palsy

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Abstract

Background: Intronic variant rs564309 in *TRIM11* is associated with clinical phenotypic differences in Progressive Supranuclear Palsy (PSP), whereby the minor allele (A) is more common in atypical PSP than typical PSP (PSP-RS). However, rs564309 has not been investigated relative to neuropathological outcomes.

Objective: Evaluate the association of rs564309 with neuropathologically-assessed severity of tau pathology, as measured by semi-quantitative scores for neurofibrillary tangles (NFT), tufted astrocytes (TA), neuropil threads (NT), and oligodendroglial coiled bodies (CB).

Methods: 797 neuropathologically-confirmed PSP cases were genotyped for *TRIM11* rs564309 and assessed for tau pathology across 20 neuroanatomical regions. Tau pathology measures and age at death (AAD) were examined for association with *TRIM11* rs564309-A using multivariable linear regression models.

Results: *TRIM11* rs564309-A was associated with increased NFT pathology (P=0.050), but was not significantly associated with AAD, NT, CB, or TA tau pathology scores.

Conclusions: *TRIM11* rs564309 may influence burden of NFT tau pathology in PSP; further study is warranted.

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Authors' Roles

Rebecca R. Valentino led the project, data analysis, and interpretation, and wrote the manuscript.

Shunsuke Koga prepared pathological tissue and analysed samples, providing tau pathology measures from across 17-20 neuroanatomical regions.

Michael G. Heckman, Danielle E. Brushaber, and Nancy N. Diehl conducted, and are responsible for, all statistical analysis.

Ronald L. Walton genotyped all the PSP samples.

Dennis W. Dickson (DWD) prepared pathological tissue and analysed samples, providing tau pathology measures from across 17-20 neuroanatomical regions.

Owen A. Ross was lead of the project and takes responsibility for the integrity of the data and the accuracy of the data analysis.

All authors were involved with the review and critique process of the manuscript.

Keywords

Progressive supranuclear palsy; TRIM11; genetics; neuropathology; tau pathology

Introduction

Progressive supranuclear palsy (PSP) is a rare, rapidly progressive, sporadic-onset neurodegenerative disease[1]. PSP is a tauopathy characterised by aggregates of an isoform of microtubule-associated protein tau, encoded by *MAPT*, which contains four microtubule-binding repeats (4R)[2]. The hyperphosphorylated molecules form neurofibrillary tangles (NFT), tufted astrocytes (TA), neuropil threads (NT), and oligodendroglia coiled bodies (CB) in the neostriatum, globus pallidus, substantia nigra, subthalamic nucleus, brain stem nuclei, and motor cortex, causing neuronal loss[1].

Clinically, typical PSP is diagnosed when patients present with vertical supranuclear gaze palsy plus postural instability and falls within the first year of symptom onset, and is usually referred to as Richardson's syndrome (PSP-RS)[1, 3–5] PSP-RS accounts for approximately 54% of all PSP cases, and is representative of PSP pathology, however atypical PSP also occurs, often with parkinsonism (PSP-P).

Differences in the location and severity of pathogenic tau accumulations in neuroanatomical regions account for changes in clinical subtype presentations[6], and recently Jabbari *et al.* reported a strong association between the minor allele (A) of intronic variant rs564309 in *TRIM11* and an increased likelihood of PSP non-RS versus PSP-RS[7]. *TRIM11* codes for an E3 ubiquitin-protein ligase which promotes the degradation of insoluble ubiquitinated proteins, and localises to the nucleus and cytoplasm. TRIM11 includes three zinc-binding domains, a RING, a type 1 and type 2 B-box, and a coiled-coil region, and is predominantly expressed in neurons, in the cerebellum and basal ganglia.

As *TRIM11* is involved in ubiquination of aberrant and regulatory proteins, and *TRIM11* rs564309 has been reported to influence clinical phenotypes of PSP, in the current study we sought to investigate whether *TRIM11* rs564309 is associated with tau pathology severity of NFT, TA, CB, and NT in PSP cases.

Methods

Study Design and Participants

This study was approved by the Mayo Clinic Institutional Review Board and individual written consent was obtained from all subjects, or their next of kin. A total of 797 pathologically-confirmed, unrelated PSP cases of European descent were included. PSP samples were donated to the Mayo Clinic (official PSP Society) brain bank for neurodegenerative disorders between 1998 and 2016 and were assessed by a single neuropathologist (DWD) following published criteria[3]. Demographics are summarised in Table 1. Exploratory retrospective clinical diagnoses were based on review of available medical records. In this study, we categorized the patients into two entities: PSP-RS (N=596) and non-RS (N=201). Age at onset (AAO) information was available for 404 cases.

Neuropathological Assessment

Semi-quantitative tau pathology scores (TPS) were determined for NFT, CB, TA, and NT tau pathology from 17-20 different neuroanatomical regions (Supplementary Table 1), using a four-point severity scale (0=none, 1=mild, 2=moderate, and 3=severe)[8]. Overall TPS were generated for each separate tau pathology measure (Supplementary Table 2), and mean overall TPS were calculated for each PSP patient across all neuroanatomical regions, whereby a higher overall score indicated more severe tau pathology. PSP patients without a TPS in a given region for a given tau pathology measure had their scores imputed by using the mean of the values of the patients who did have scores. Patients were removed from analysis for a given overall TPS if they had >50% missing data across neuroanatomical regions for the given measure. 713 cases were additionally assessed for Alzheimer-type pathology (Braak NFT stage[9] and Thal amyloid phase[10]) with thioflavin S fluorescent microscopy[11, 12] (Table 1).

Sample Preparation and Genotyping

Genomic DNA was isolated from frozen cerebral brain tissue from PSP cases using Autogen 245T (Holliston, MA) methods. *TRIM11* variant rs564309 was genotyped using a TaqMan Allelic Discrimination Assay (Assay ID: C __1172993_10) on a QuantStudio™ 7 Flex Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) and genotypes were called using QuantStudio™ Real-Time PCR Software (v1.1). No evidence of deviation from Hardy-Weinberg equilibrium (P=0.92) was observed.

Statistical Analysis

Associations of *TRIM11* rs564309 with age at death (AAD), AAO, early-onset PSP (EOPSP) (≤55 years old), overall TPS, and clinical subtype were evaluated using multivariable linear and binary logistic regression models. Models were adjusted for sex in AAD, AAO, and EOPSP analysis; AAD, sex, Braak stage, and Thal phase in overall TPS analysis; and AAD and sex in clinical subtype analysis. Associations of rs564309 with semi-quantitative TPS in individual neuroanatomical regions were evaluated using proportional odds logistic regression models that were adjusted for AAD, sex, Braak stage, and Thal phase. Comparisons of characteristics between the RS and non-RS subtypes were made using a Wilcoxon rank sum test or Fisher's exact test in unadjusted analysis. In adjusted analysis, these comparisons were made using multivariable linear regression models (AAD, AAO, and TPS analysis), binary logistic regression models (sex and EOPSP), and proportional odds logistic regression models (Braak stage and Thal phase analysis). No adjustment for multiple testing was made, and p-values ≤0.05 were considered statistically significant. Statistical analyses were performed using SAS (version 9.4).

Results

TRIM11 rs564309 genotypes were homozygous wildtype (C/C) in 662 (83.1%), heterozygous (C/A) in 129 (16.2%), and homozygous mutant in 6 (0.8%) cases respectively, resulting in a minor allele frequency (MAF) of 8.8% (9.0% PSP-RS; 8.5% non-RS). Associations of *TRIM11* rs564309 with PSP clinical subtype, AAO, EOPSP, overall TPS, and AAD are displayed in Table 2. There was a statistically significant association between

presence of the rs564309 minor allele and a more severe overall NFT TPS (P=0.050, Supplementary Figure 1A). A similar, but non-significant, finding was observed for overall NT TPS (P=0.098, Supplementary Figure 1B). rs564309 was not associated with AAO, EOPSP, clinical subtype, AAD, overall CB TPS, or overall TA TPS (all P≥0.60, Table 2).

Given the significant association between *TRIM11* rs564309 and overall NFT TPS, we next assessed associations in individual neuroanatomical regions, acknowledging power to detect associations is lower than when examining overall TPS (Supplementary Table 3). Presence of the rs564309 minor allele was associated with more severe NFT tau pathology in the locus coeruleus (LC) (OR=1.84, P=0.009) and medullary tegmentum (MT) (OR=1.77, P=0.027) regions, with similar, but not quite significant, associations observed for the globus pallidus (GP) (OR=1.43, P=0.052) and basal nucleus (BN) (OR=1.48, P=0.059).

In a secondary analysis, comparing characteristics between the RS and non-RS subtypes, AAD and AAO were significantly older for the non-RS cases (P<0.001). NT TPS was also slightly higher in non-RS cases in adjusted analysis (P=0.030). There were no other noticeable differences between RS and non-RS cases (Supplementary Table 4).

Discussion

Intergenic variant rs564309 in *TRIM11* has recently been associated with the clinical phenotype of PSP, whereby non-RS individuals carried a significantly higher frequency of the minor allele than PSP-RS patients[7] and EOPSP cases carried a significantly higher frequency of rs564309-A compared to late-onset PSP[13]. These observations did not replicate in our cohort which may be due to variation between clinical phenotype methodologies between studies. The degree to which *TRIM11* rs564309 is associated with neuropathological features of PSP has not been previously studied. Our results indicate that *TRIM11* rs564309 is associated with a mildly increased overall NFT severity and possibly a greater NT severity. No significant associations were observed for CB or TA tau pathology, or AAD.

TRIM11 codes for an E3 ubiquitin-protein ligase which is a key regulator of the ubiquitination pathway, removing aberrant proteins and maintaining the cellular proteosome. NFT are intracellular, lesions composed of dense, filamentous, aggregated hyperphosphorylated tau proteins which commonly appear in neurons in the basal ganglia, diencephalon, and brainstem in PSP[14]. NT are abnormal neurites consisting of straight and paired helical filaments of tau and ubiquitin which predominantly aggregate in the basal ganglia, internal capsule, and thalamic fasciculus. NFTs are primarily formed from 4R tau inclusions[15, 16], and given PSP is a 4R tauopathy[2, 17], more severe NFT pathology is expected to be observed.

rs564309 is located in the *TRIM11* intronic region, and particularly high levels of *TRIM11* are expressed in the cerebellum and putamen from neurologically-healthy brains[7]. As significantly higher levels of NFT are associated with rs564309-A in our study, the minor allele may be interrupting *TRIM11* transcription, which may be decreasing TRIM11 protein levels and preventing aberrant protein clearance, therefore accelerating NFT pathology.

TRIM11 RNA expression, and additional protein quantification, needs to be determined in diseased brains to clarify the effect rs564309 has on TRIM11 in PSP. Furthermore, to determine if rs564309 is driving NFT severity in tauopathies, a replication study in neuropathological AD brains could be conducted because, albeit different distribution patterns, similar tau epitopes are found in NFTs in PSP and Alzheimer's disease (AD) brains[18]. Moreover, *TRIM11* is predominantly expressed neuronally, particularly in the cerebellum and basal ganglia, which may explain why *TRIM11* is associated with increased NFT pathology and potential NT pathology but not TA and CB, which predominantly compose glial lesions in the motor cortex, striatum, and white matter respectively[15]. The combination of tau pathology localisation and *TRIM11* expression differences may explain why associations were only reported in NFT, and potentially NT, in this study.

Our data additionally reports significantly increased NFT tau pathology in LC and MT for rs564309-A carriers[1]. Our results indicate that, that regardless of statistical significance, *TRIM11* rs564309 is associated with elevated (OR>1) NFT TPS in 16 of the 18 neuroanatomical regions assessed. This suggests that the association between *TRIM11* rs564309 and overall NFT TPS is not driven by strong associations in a few regions, but instead by milder, and fairly consistent, associations across brain regions. Interestingly, overall tau burden is also higher in PSP-RS patients[6], although in our cohort we did not observe a clear pathologic distinction between the clinical subtypes. It will be important to validate these findings as we did not adjust for multiple testing; however, the moderate degree of correlation between the four TPS's alleviates this concern somewhat. Additionally, without available genome-wide control markers, population stratification could have had an impact on our results.

In conclusion, our data does not support the previous finding of a higher frequency of rs564309-A in non-RS sufferers compared to PSP-RS reported by Jabbari *et al.*[7], highlighting the need for further study of this *TRIM11* variant in relation to PSP subtype. Our data does however suggest that the minor allele is associated with a slight but significant increase in the severity of NFT pathology. Though replication of these findings will be crucial, it will also be important to further understand the functional mechanisms involved in TRIM11 signalling and its potential influence on disease clinical/pathologic heterogeneity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Summary of PSP patient characteristics (N=797). The sample median (minimum, maximum) is provided for continuous variables. Information was unavailable for N=1 CB tau pathology score, N=31 TA tau pathology score, and N=1 NT tau pathology score.

Variable	PSP cases (N=797)
Age at PSP onset (years)[1]	68 (46, 90)
Early onset PSP (≤55 years)[1]	34 (8.4%)
Age at death (years)	75 (52, 98)
Sex	
Male	423 (53.1%)
Female	374 (46.9%)
Clinical subtype	
Richardson	596 (74.8%)
Non-Richardson	201 (25.2%)
Braak stage	
0	117 (14.7%)
I	133 (16.7%)
II	234 (29.4%)
III	247 (31.0%)
IV	50 (6.3%)
V	10 (1.3%)
VI	6 (0.8%)
Thal phase	
0	355 (44.5%)
1	132 (16.6%)
2	54 (6.8%)
3	194 (24.3%)
4	43 (5.4%)
5	19 (2.4%)
CB tau pathology score	1.51 (0.25, 2.36)
NFT tau pathology score	2.23 (0.83, 2.89)
TA tau pathology score	0.99 (0.06, 2.06)
NT tau pathology score	2.15 (0.35, 2.90)

[1]Indicates data available for N=404 PSP cases. CB=coiled bodies; NFT=neurofibrillary tangles; TA=tufted astrocytes; NT=neuropil threads.

Table 2:

Association of *TRIM11* variant rs564309 with non-Richardson clinical subtype, age at PSP onset, early-onset PSP (≤55 years old), CB, NFT, TA, and NT pathology scores and age at death (years). The association between *TRIM11* rs564309 and non-Richardson clinical subtype and early-onset PSP were evaluated using a logistic regression model that was adjusted for age at death (only non-Richardson clinical subtype) and sex. The odds ratio is interpreted as the multiplicative increase in the odds of the given outcome corresponding to presence of the minor allele (A) of *TRIM11* rs564309. Associations of *TRIM11* rs564309 with tau pathology scores result from linear regression models that were adjusted for age at death, sex, Braak stage, and Thal phase. The associations of *TRIM11* rs564309 with age at PSP onset and age at death result from linear regression models that were adjusted for sex. Regression coefficients are interpreted as the increase in the mean outcome measure corresponding to presence of the minor allele (A) of *TRIM11* rs564309. CB=coiled bodies; NFT=neurofibrillary tangles; TA=tufted astrocytes; NT=neuropil threads; CI=confidence interval.

		Association with *TRIM11* rs564309	
Outcome measure	**Association measure**	**Estimate (95% CI)**	**P-value**
Non-Richardson clinical subtype	Odds ratio	0.96 (0.62, 1.48)	0.84
Age at PSP onset	Regression coefficient	0.55 (−1.52, 2.62)	0.60
Early-onset PSP (≤55 years)	Odds ratio	1.06 (0.42, 2.65	0.91
CB tau pathology score	Regression coefficient	0.01 (−0.05, 0.07)	0.78
NFT tau pathology score	Regression coefficient	0.06 (0.00, 0.12)	0.050
TA tau pathology score	Regression coefficient	0.00 (−0.07, 0.07)	0.99
NT tau pathology score	Regression coefficient	0.06 (−0.01, 0.13)	0.098
Age at death	Regression coefficient	−0.18 (−1.58, 1.22)	0.80