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Psychotic symptoms in frontotemporal dementia with TDP-43 tend to be associated with type B pathology

Veronica Hirsch-Reinshagen[1] | Christa Hercher[2,3] | Fidel Vila-Rodriguez[3] | Manuela Neumann[4,5] | Rosa Rademakers[6,7] | William G. Honer[3,8] | Ging-Yuek R. Hsiung[9] | Ian R. Mackenzie[1]

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada

[2]Douglas Mental Health University Institute, McGill University, Montreal, Canada

[3]Department of Psychiatry, University of British Columbia, Vancouver, Canada

[4]Molecular Neuropathology of Neurodegenerative Diseases, German Center for Neurodegenerative Diseases, Göttingen, Germany

[5]Department of Neuropathology, University Hospital of Tübingen, Tübingen, Germany

[6]Applied and Translational Neurogenomics, VIB Center for Molecular Neurology, Edegem, Belgium

[7]Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium

[8]BC Mental Health and Substance Use Disorders Research Institute, Vancouver, Canada

[9]Division of Neurology, University of British Columbia, Vancouver, Canada

Correspondence
Veronica Hirsch-Reinshagen, Department of Pathology, Vancouver General Hospital, 855 West 12th Avenue, Vancouver, British Columbia V5Z 1M9, Canada.
Email: veronica.hirsch@vch.ca

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Abstract

Aims: Psychotic symptoms are increasingly recognized as a distinguishing clinical feature in patients with dementia due to frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP). Within this group, carriers of the *C9orf72* repeat expansion are particularly prone to develop delusions and hallucinations.

Methods: The present retrospective study sought to provide novel details about the relationship between FTLD-TDP pathology and the presence of psychotic symptoms during life.

Results: We found that FTLD-TDP subtype B was more frequent in patients with psychotic symptoms than in those without. This relationship was present even when corrected for the presence of *C9orf72* mutation, suggesting that pathophysiological processes leading to the development of subtype B pathology may increase the risk of psychotic symptoms. Within the group of FTLD-TDP cases with subtype B pathology, psychotic symptoms tended to be associated with a greater burden of TDP-43 pathology in the white matter and a lower burden in lower motor neurons. When present, pathological involvement of motor neurons was more likely to be asymptomatic in patients with psychosis.

Conclusions: This work suggests that psychotic symptoms in patients with FTLD-TDP tend to be associated with subtype B pathology. This relationship is not completely explained by the effects of the *C9orf72* mutation and raises the possibility of a direct link between psychotic symptoms and this particular pattern of TDP-43 pathology.

KEYWORDS
ALS, frontotemporal dementia, FTLD-TDP, histology, psychosis

INTRODUCTION

Frontotemporal dementia (FTD) is a heterogeneous clinical syndrome characterised by progressive abnormalities of personality, behaviour and/or language with relative preservation of memory. FTD is the second most common type of early-onset dementia and is most commonly caused by frontotemporal lobar degeneration (FTLD), a heterogeneous group of pathologies that result in prominent atrophy of the frontal and temporal lobes [1]. FTLD is subclassified based on the identity of the protein that accumulates in pathological inclusions in neurons and glia. The most common subtype of FTLD is characterised by cellular inclusions of TAR DNA-binding protein 43 (TDP-43) and is termed FTLD-TDP [1, 2]. In addition to FTLD, pathological TDP-43 inclusions have also been described in the vast majority of patients with sporadic and inherited forms of amyotrophic lateral sclerosis (ALS) [3]. Clinical overlap between FTD and ALS [4, 5] and involvement of extra-motor areas by TDP-43 pathology in clinically pure ALS cases have been well documented [6, 7]. This supports the concept that FTLD-TDP and ALS-TDP lie at the ends of a disease spectrum characterised by clinical, genetic and pathological commonalities.

FTLD-TDP can be subdivided into four or five main histological subtypes based on the type, morphology, neocortical laminar and subcortical distribution of TDP-43 immunoreactive pathological changes [8–11]. These neuropathological subtypes show remarkable correlations with specific genetic mutations and clinical phenotypes [2]. The most frequent types of FTLD-TDP are A, B, C and mixed A + B [8, 12–14], the latter designation being given to cases that show typical features of both types A and B [14, 15]. According to current criteria [8, 14], FTLD-TDP type A is characterised by moderate to abundant compact neuronal cytoplasmic inclusions (NCI), moderate to abundant short dystrophic neurites (DN) and occasional neuronal intranuclear inclusions, all concentrated in neocortical layer II. Type B shows moderate to abundant, predominantly granular, NCI in all neocortical layers, while type C typically exhibits many long thick DN. Although consensus diagnostic criteria for each subtype are published and widely applied [8], the interrater agreement is variable [16]. This variability is partly explained by methodological issues associated with immunohistochemical procedures [16].

In addition to the neocortical features described above, each subtype has characteristic subcortical patterns of involvement [15, 17]. Type A is associated with abundant thread pathology in white matter and subcortical grey matter regions and delicate TDP-43 threads in CA1. Type B cases show a predominance of glial cytoplasmic inclusions (GCI) in the cerebral white matter, diffuse granular NCI in subcortical grey matter and, most characteristically, NCI in lower motor neurons (LMN). Type C has minimal involvement of subcortical structures apart from compact Pick body-like NCI in the hippocampal dentate layer and the striatum [15, 17]. Inclusion of these subcortical features may help disambiguate or confirm mixed features in cases with borderline or mixed neocortical patterns [16, 18, 19] or in cases due to *C9orf72* mutations, the latter of which are known to be more difficult to classify [15].

Key points

- FTLD-TDP type B pathology tends to be more frequent in patients with psychotic symptoms than in those without.
- This relationship is only partially explained by the association of type B pathology with *C9orf72* hexanucleotide expansion.
- Within subjects with FTLD-TDP type B pathology, psychotic symptoms tended to be associated with a greater burden of TDP-43 pathology in the white matter and a lower burden in lower motor neurons.

Notably, each FTLD-TDP subtype has prototypic clinical and genetic phenotypes that, if understood at the pathophysiological level, could yield important insights into the unique cellular types and processes affected in each of these pathological subtypes. For example, patients with FTLD-TDP type A are more prone to develop nonfluent primary progressive aphasia (nfvPPA) and/or parkinsonism and are genetically linked to mutations in the progranulin gene (*GRN*) [2]. Type B cases are typically associated with ALS in the context of bvFTD and are genetically linked to hexanucleotide repeat expansion in the *C9orf72* gene [2], while type C cases have a strong association with the semantic variant of PPA (svPPA) and are usually sporadic [2].

Psychotic symptoms such as delusions and/or hallucinations are generally uncommon in the FTD patient population, affecting less than 10% of all FTD cases [20, 21]. Nonetheless, certain subgroups of patients with FTD, including those with underlying TDP-43 pathology [22, 23] and those carrying the *C9orf72* repeat expansion [24–30], have a much higher prevalence of these symptoms, with some reports describing psychotic symptoms in up to 50% of patients with *C9orf72* mutations [24, 25, 28, 31]. Furthermore, the presence of hallucinations has been found to be a discriminatory feature between FTLD-TDP and other FTLD pathologies [32].

While the precise neuroanatomical correlates of psychotic symptoms are not fully elucidated, neuroimaging studies using different modalities converge onto several regions of interest. Structural MRI studies have shown that multiple cortical regions including bilateral prefrontal, temporoparietal, superior temporal, inferior frontal areas and limbic cortex are affected in patients with primary psychotic disorders and with psychotic symptoms in *C9orf72* mutation carriers [33, 34]. Subcortically, patients with primary psychotic disorders such as schizophrenia have been shown to have smaller hippocampus, amygdala, thalamus and nucleus accumbens, as well as larger pallidum and lateral ventricle volumes [35]. Finally, evaluations using diffusion MRI have also shown white matter abnormalities in psychotic disorders, suggesting potential abnormalities in brain structural connectivity [36].

Given the higher incidence of psychotic symptoms in patients with FTLD-TDP, we sought to further define the relationship between neocortical FTLD-TDP subtypes and their associated subcortical pathology and psychotic symptomatology. To this end, the presence of delusions, hallucinations, and paranoia in retrospectively reviewed clinical charts of autopsy-confirmed FTLD-TDP cases was correlated with neocortical FTLD-TDP subtype and subcortical involvement.

MATERIALS AND METHODS

Cases

This study was performed in accordance with institutional ethical standards, including informed consent of the individual participant and/or legal representative. The University of British Columbia (UBC), Canada, research brain bank contains more than 100 cases with clinical history of dementia and post-mortem confirmation of primary FTLD-TDP pathology. Inclusion criteria required the availability of complete neurological notes from behavioural neurologists at the UBC Clinic for Alzheimer Disease and Related Disorders, which were available for 54 cases from 1988 onwards. Four additional cases with psychotic symptoms from the Brain Bank associated with the DZNE and the University of Tübingen, Germany, were also included. The exclusion criteria were the presence of severe AD (high level of Alzheimer's disease neuropathologic change as per NIA-AA criteria [37]) or significant alternate neurodegenerative pathologies on post-mortem evaluation. Most of these cases were included in previously reported cohorts [14, 15].

Patients were clinically evaluated at the time of presentation and followed up yearly until they were admitted to long-term care facilities. Clinical charts were reviewed for the presence and type of comorbid psychiatric symptoms by an investigator (VHR) blinded to the FTLD-TDP subtype and genetic status of the patient. Cases that were more difficult to classify from a clinical perspective were reviewed in consultation with a psychiatrist (FVR).

Genetic evaluation

All cases were evaluated for the presence of the *C9orf72* mutation, either by genetic analysis or by histological evaluation for the presence of dipeptide repeats (DPR), yielding 24 positive cases. Of the remaining 34 non-*C9orf72* cases, 27 cases had genetic testing for other common FTLD-TDP-causing mutations as described previously [37]. The test results for these cases are summarised in Table S1.

Pathology

A standard neuropathological evaluation was performed in all cases, including the evaluation of non-TDP-43 neurodegenerative conditions. Cases included in this study had at most stage Braak IV neurofibrillary pathology with no more than moderate numbers of senile neuritic plaques (classified as moderate Alzheimer's disease [AD] and corresponding to an intermediate level of Alzheimer's disease neuropathologic change using NIA-AA criteria [38]). Only one case had significant comorbid Lewy-related pathology (diffuse neocortical type [39] or Braak stage 5 [40]). This case did not exhibit psychotic symptoms.

For the evaluation of FTLD-TDP pathology subtype, immunohistochemistry with a phosphorylation-independent TDP-43 primary antibody (ProteinTech Group anti-TARDBP; 1:1000) was performed on 5-μm-thick sections of the frontal neocortex, cerebral white matter, hippocampus, striatum, midbrain, medulla and, where available, spinal cord. Evaluation of the neocortical FTLD-TDP pathology included semiquantitative assessment of different types of TDP-43 immunoreactive cellular inclusions (NCI, DN, GCI, threads) and total pathology burden in superficial and deep neocortical laminae of the frontal cortex as per current guidelines [8, 14]. Subcortical FTLD-TDP pathology evaluation was performed on sections of cerebral white matter, hippocampal dentate and CA1 region, striatum, substantia nigra, hypoglossal nucleus and spinal cord ventral grey matter (when available) [8, 14, 15] The cases were assigned neocortical and subcortical A, B, AB and C types. Our cohort did not include unequivocal FTLD-TDP type E cases.

Statistics

Two-tailed Fisher's exact test was used to evaluate differences in proportions between groups. Two-tailed *T*-tests and Mann–Whitney tests were used for the evaluation of continuous and ordinal variables between groups, respectively. The significance level was set at $p < 0.05$. Binomial logistic regression analysis with psychosis as the dependent variable and sex, age of onset, disease duration, neocortical FTLD-TDP type (B/non-B), genetics (C9/non-C9), clinical motor neuron disease (MND, present/absent) and pathological LMN TDP-43 inclusions (present/absent) was performed to identify significant contributing factors.

RESULTS

Clinical characteristics and genetics

Details of the demographic, clinical, genetic and pathological characteristics of our study cohort are presented in Table S1. Within the entire cohort of 58 patients with complete clinical notes, 19 (33%) had significant psychotic and/or paranoid symptomatology. Fifteen of these had delusions, with or without hallucinations, of enough severity to be identified during routine neurological interviews or as presenting symptoms. Four additional cases had prominent paranoia, bordering on persecutory delusions. Of note, these patients were evaluated by specialists in behavioural neurology, and most did not have extensive psychiatric evaluations. The remaining 39 cases

displayed either no psychiatric symptoms or variable degrees of obsessive, depressive or aggressive symptoms. A summary of the demographic, clinical and genetic characteristics of our cohort is presented in Table 1. Sex distribution, age at onset and disease duration were not significantly different between cases with or without psychotic symptoms. The percentage of clinically recognised ALS was also not different between the groups (Table 1).

Of the 19 patients with psychotic symptoms, 11 (58%) had positive genetic testing or histological features (DPR inclusions) for an underlying *C9orf72* repeat expansion. Of the remainder eight non-*C9orf72* cases, one patient had a *GRN* mutation, one had a *UBQLN2* mutation, five had no mutations identified and one did not have genetic testing. Of note, the patient with psychotic symptoms and a *GRN* mutation developed delusions in her 20s and was diagnosed with a psychotic disorder in her 30s, approximately 20 years prior to developing language impairments and semantic dementia. In contrast to the patients with psychotic symptoms, only 13 (33%) of those without psychosis had positive genetic testing or histological features for an underlying *C9orf72* mutation. Of those without psychotic symptoms, 11 carried pathogenic mutations in *GRN* ($N = 8$), *TIA1* ($N = 2$) and *TBK1* genes ($N = 1$), while nine were negative for common FTLD mutations, and six did not have genetic testing. In line with prior published reports [24, 25, 28, 31], these data suggest that *C9orf72* mutations are more frequent in those with psychotic symptoms than those without, though this difference did not reach statistical significance in our cohort. In addition, 11 out of 24 of the patients carrying a *C9orf72* mutation developed psychotic symptoms, whereas only one out of nine of those with a *GRN* mutation had such symptoms in our cohort.

TABLE 1 Summary of demographic, clinical and genetic characteristics.

	Psychotic symptoms	No psychotic symptoms
Sex (F/M), *n*	9/10	19/20
Age at onset years, mean (SD)	57.7 (9.9)	57.6 (10.4)
Illness duration years, mean (SD)	7.1 (3.5)	5.9 (4.2)
C9orf72 carrier, per cent	58%	33%
Clinical ALS	26%	38%
Asymptomatic LMN pathology	56%*	21%*

Abbreviations: ALS, amyotrophic lateral sclerosis; F, female; LMN, lower motor neuron; M, male; *n*, number; SD, standard deviation.
*$p = 0.03$ two-tailed Fisher's exact test.

TABLE 2 Neocortical FTLD-TDP subtypes in patients with and without psychotic symptoms.

Neocortical subtype	Psychotic symptoms	No psychotic symptoms
Subtype A, *n* (per cent)	2 (11%)	10 (26%)
Subtype B, *n* (per cent)	9 (47%)	16 (42%)
Subtype AB, *n* (per cent)	7 (37%)	6 (16%)
Subtype C, *n* (per cent)	1 (5%)	6 (16%)
Subtype B + AB, *n* (per cent)	16 (84%)	22 (58%)
Total, *n*	19	38

Neuropathology

The proportion of *neocortical* FTLD-TDP types A, B, AB and C in cases with psychotic symptoms was 11%, 47%, 37% and 5%, respectively (Table 2), whereas in those without psychosis, these proportions were 26%, 42%, 16% and 16%. The distribution of *subcortical* types (A, B, AB and C) in cases with and without psychotic symptoms was similar to that of neocortical types: 16%, 47%, 32% and 5% vs 32%, 39%, 13% and 16% in nonpsychotic cases, respectively. The increased frequencies of type B and AB pathology in patients with psychotic symptoms vs those without were not statistically significant when each group was considered separately. When cases were dichotomized into those with any type B pathology (i.e., either pure B or AB) and those with no type B pathology (those with either pure type A or C), we found that type B pathology showed a trend to be overrepresented in those with psychotic symptoms (84% neocortical and 79% subcortical, respectively) compared with those without (58% neocortical and 53% subcortical, respectively) (Table 2; $p = 0.07$ two-tailed Fisher's exact test).

Because the *C9orf72* repeat expansion is associated with psychotic symptoms and most often has type B or AB pathology, we sought to understand whether the association of type B pathology with psychosis was entirely due to the influence of the *C9orf72* mutation. We found that type B pathology was also more common in non-*C9orf72* patients with psychotic symptoms (6/8, 75%) compared with those without (10/26, 38%), although the numbers of cases were too low to reach statistical significance. Binomial logistic regression analyses (Table 3) showed that type B pathology was the factor with the largest effect size and the only statistically significant element in three models with different combinations of factors including TDP subtype, C9 status, sex, age of onset, disease duration and clinical MND. Together, this suggests that the presence of psychotic symptoms is associated with FTLD-TDP type B pathology to a greater extent than that attributable to the *C9orf72* mutation.

In an attempt to elucidate an anatomical and/or cellular substrate for delusions and hallucinations, we compared the severity of TDP-43 pathology in different neocortical laminae, limbic and subcortical regions in FTLD-TDP type B cases with and without psychotic symptoms (Figure 1) [14, 15]. None of these measures showed a statistically significant difference between groups, although there was a

TABLE 3 Binomial logistic regression models.

Model 1				
Model coefficients—psychosis				
Predictor	**Estimate**	**SE**	***Z***	***p***
Intercept	2.2681	2.1489	1.055	0.291
Onset	−0.0340	0.0335	−1.015	0.310
Duration	−0.1006	0.1064	−0.945	0.345
C9orf72				
No—yes	0.5573	0.7257	0.768	0.443
B type (neocortical)				
No—yes	2.1459	1.0226	2.099	**0.036**
Clinical MND				
Yes—no	1.1678	0.8709	1.341	0.180
Sex				
F—M	−0.6099	0.7253	−0.841	0.400
Model 2				
Model coefficients—psychosis				
Predictor	**Estimate**	**SE**	***Z***	***p***
Intercept	1.7829	2.0386	0.875	0.382
C9				
No—yes	0.5502	0.7176	0.767	0.443
B type (neocortical)				
No—yes	1.8917	0.9474	1.997	**0.046**
Clinical MND				
Yes—no	0.8917	0.7926	1.125	0.261
Onset	−0.0285	0.0328	−0.869	0.385
Duration	−0.0947	0.1006	−0.941	0.347
Model 3				
Model coefficients—psychosis				
Predictor	**Estimate**	**SE**	***Z***	***p***
Intercept	1.3162	1.8826	0.699	0.484
C9orf72				
No—yes	0.7679	0.6934	1.107	0.268
B type (neocortical)				
No—yes	1.8991	0.9605	1.977	**0.048**
Clinical MND				
Yes—no	1.4586	0.8139	1.792	0.073
Onset	−0.0307	0.0327	−0.939	0.348
Sex				
F—M	−0.5891	0.7063	−0.834	0.404

Note: Estimates represent the log odds of "Psychosis = no" vs "Psychosis = yes." Bold values indicate *p* values < 0.05.

trend for cases with psychotic symptoms to have more severe pathology in the cerebral white matter and fewer inclusions in LMN (cranial nerve XII and spinal cord motor neurons), especially in the spinal cord. Indeed, a statistically larger number of patients with asymptomatic LMN involvement (TDP-43 pathology in LMN without a clinical diagnosis of MND) was identified in the group with psychotic symptoms (10/19, 56%) than in those without (8/38, 21%; Table 1; $p = 0.03$ two-tailed Fisher's exact test) irrespective of pathological subtype and even after controlling for *C9orf72* carrier status. This would raise the possibility that the pathophysiological processes that increase the risk for the development of psychotic symptoms may, at the same time, result in a higher likelihood of subclinical LMN pathology.

DISCUSSION

This study addressing the correlation between FTLD-TDP pathological subtypes and associated subcortical involvement with psychotic symptoms showed that psychotic symptomatology is associated with underlying FTLD-TDP subtype B pathological features, which is only partially explained by the known association of *C9orf72* mutations with both subtype B pathology and psychosis [2, 24, 25, 28, 31]. This is consistent with previous studies showing that patients with psychosis and autopsy-confirmed FTLD-TDP, including familial and sporadic cases, have a higher proportion of subtype B than A pathology [23, 26]. A more recent study found a correlation between the rare FTLD-TDP type E pattern and neuropsychiatric symptoms [32]. An additional report showed the same prevalence of psychotic symptoms in type A and type B FTLD-TDP [41], although this cohort contained more *C9orf72* mutation carriers classified as type A than ours. The greater proportion of FTLD-TDP type A among *C9orf72* mutation carriers in the latter study and the fact investigators in one study consider FTLD-TDP type E to be a variant of type B [42] may be explained, at least partly, by interrater variability in FTLD-TDP typing among neuropathologists [16].

Although analysis of other subcortical pathological features in our cohort did not confirm the recently reported association between hallucinations and TDP-43 pathology burden in the granular cell layer of the hippocampus [32], our previous studies have shown that, on average, FTLD-TDP type B pathology is associated with more granule layer pathology than either A or C [15]. Detailed analysis of the results of this study also revealed that rather than the overall TDP-43 pathology burden in subcortical regions it is the frequency of individual pathological features in each region that is different between types. For example, the total burden of striatal TDP-43 pathology is not significantly different between types; however, type B has significantly more diffuse NCI and GCI than A or C, whereas A has more NII and C shows the greatest amount of compact NCI compared with other types [15]. This suggests that although all subtypes affect the CNS diffusely, each one is likely associated with different pathophysiological processes that result in distinct morphological patterns of inclusions.

The association between the histological involvement of LMNs, a salient subcortical feature associated with type B pathology [15, 17] and psychotic symptoms has also been identified at the clinical level. Relatives of patients with ALS are at higher risk of developing psychotic disorders, a trait that is pronounced in kindreds carrying a *C9orf72* mutation, but is also present in those without [43]. Genetic

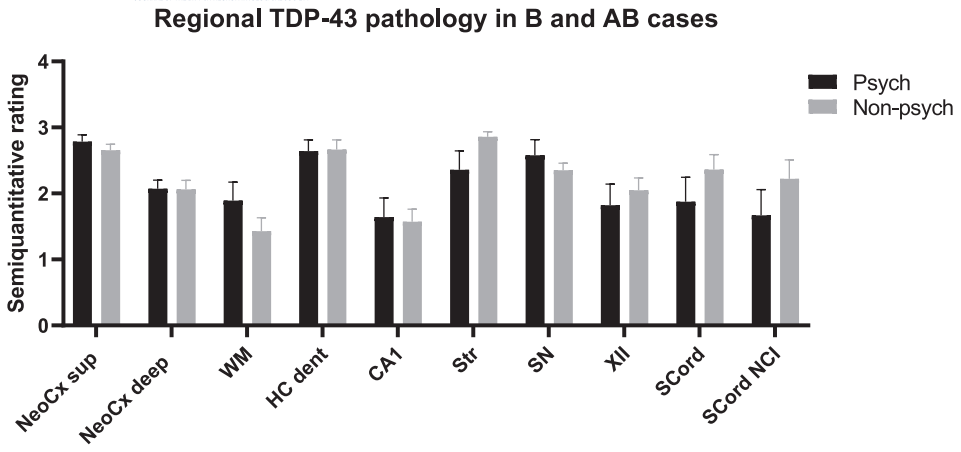

FIGURE 1 Semiquantitative rating of TDP-43 immunoreactive pathology in cases with type B and AB pathology with and without psychotic symptoms. No significant differences were identified, although cases with psychotic symptoms showed a tendency to more severe white matter pathology and less severe involvement of lower motor neurons. CA1: Hippocampal CA1 region; HC dent: Hippocampal dentate fascia; NCI: Neuronal cytoplasmic inclusions; NeoCx: Neocortex; SN: Substantia nigra; Str: Striatum; SCord: Spinal cord; Sup: superficial; WM: White matter; XII: Hypoglossal nucleus.

analysis using genome-wide association study data from over 100,000 unique individuals revealed a genetic correlation between ALS and schizophrenia, which would result in a modest increase in comorbidity between ALS and schizophrenia [44]. Together, this suggests that the pathophysiological process to which LMNs are vulnerable may also affect neuronal cell types and/or circuits involved in the generation of psychotic symptoms.

It was surprising that clinical MND was less common in our patients with psychotic symptoms and that subclinical LMN involvement showed the strongest association with such symptoms, being more than twice as frequent as in patients without psychotic symptomatology (Table 1). Although this might suggest that factors that modulate the rate of progression of LMN pathology (e.g., *ATXN2* intermediate length repeats [45]) or the anatomical distribution may be inversely related to the clinical development of psychotic symptoms, it must also be considered that earlier death and antemortem morbidity of patients with ALS might reduce the opportunity for psychotic symptoms to be recognised during the disease course.

Although our cohort was evaluated pathologically in a consistent manner, only crude correlations with clinical phenotypes are possible, given the referral bias of our cohort (only dementia clinic patients) and the long period of time covered in this study over which clinical diagnostic criteria and evaluation protocols have evolved. Additionally, the standard neuropathological evaluation performed in these cases limited the range of sampled anatomical sites.

CONCLUSIONS

In summary, this work suggests that psychotic symptoms in patients with FTLD-TDP tend to be associated with type B pathology. Importantly, although this relationship is partly explained by a higher frequency of *C9orf72* carriers in patients with psychotic symptoms, the relationship extends more broadly, suggesting a direct mechanistic link to this particular pattern of TDP-43 pathology.

AUTHOR CONTRIBUTIONS

Veronica Hirsch-Reinshagen performed the analysis and wrote the manuscript. Christa Hercher and Fidel Vila-Rodriguez helped with experiments and data analysis. Manuela Neumann provided samples and data analysis. Rosa Rademakers performed the genetic analysis. William G. Honer provided resources and reviewed the manuscript. Ging-Yuek R. Hsiung helped with patient recruitment. Ian R. Mackenzie was the supervisor of the project, performed some data analysis and helped with manuscript writing.

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CONFLICT OF INTEREST STATEMENT

The authors report no competing interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/nan.12921.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ETHICS STATEMENT

This study was performed in accordance with institutional ethical standards, including informed consent of the individual participant and/or legal representative.

ORCID

Manuela Neumann https://orcid.org/0000-0002-6232-4057

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