The Canadian Journal of Neurological Sciences (2023), 1–10
doi:10.1017/cjn.2023.248

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Original Article

A Systematic Review of the Genetics and Pathology of Psychosis in Frontotemporal Dementia

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ABSTRACT: ***Objectives:*** Frontotemporal dementia (FTD) patients frequently present with psychosis, which complicates diagnosis and management. In this study, we aim to examine the relationship between psychosis and the most common genetic mutations predisposing to FTD, and in the different pathological subtypes of FTD. ***Design:*** We conducted a systematic review, searching the literature up to December 2022, and reviewed 50 articles that met our inclusion criteria. From the reviewed articles, we extracted and summarized data regarding the frequency of psychosis and patient characteristics in each major genetic and pathological subtype of FTD. ***Results:*** Among FTD patients with confirmed genetic mutations or pathological diagnosss, the frequency of psychosis was 24.2%. Among the genetic mutation carriers, *C9orf72* mutation carriers had the highest frequency of psychosis (31.4%), whereas *GRN* (15.0%) and *MAPT* (9.2%) mutation carriers had lower frequencies of psychosis. *MAPT* mutation carriers notably developed psychosis at a younger age compared to other genetic groups. The most common psychotic symptoms were delusions among *C9orf72* carriers and visual hallucinations among GRN mutation carriers. Among the pathological subtypes, 30% of patients with FUS pathology, 25.3% of patients with TDP-43 pathology, and 16.4% of patients with tau pathology developed psychosis. In the TDP-43 group, subtype B pathology was the most common subtype reported in association with psychosis. ***Conclusion:*** Our systematic review suggests a high frequency of psychosis in specific subgroups of FTD patients. Further studies are required to understand the structural and biological underpinnings of psychosis in FTD.

RÉSUMÉ : Analyse systématique de la génétique et de la pathologie psychotique dans la démence fronto-temporale. ***Objectifs :*** Les patients atteints de démence fronto-temporale (DFT) présentent souvent une psychose, ce qui complique leur diagnostic et leur prise en charge. Cette étude a pour but d'examiner la relation entre la psychose et les mutations génétiques les plus courantes qui prédisposent à la DFT. ***Conception :*** Nous avons procédé à une analyse systématique en effectuant une recherche de littérature dont la limite était décembre 2022. Nous avons ensuite examiné 50 articles qui répondaient à nos critères d'inclusion. Enfin, nous avons extrait et résumé les données relatives à la fréquence des cas de psychose et aux caractéristiques des patients, et ce, pour chaque sous-type génétique et pathologique majeur de la DFT. ***Résultats :*** Parmi les patients atteints de DFT avec des mutations génétiques confirmées ou un diagnostic pathologique, la fréquence de psychose était de 24,2 %. Parmi les porteurs de mutations génétiques, les porteurs de la mutation du gène C9orf72 présentaient la fréquence de psychose la plus élevée (31,4 %) tandis que les porteurs des mutations génétiques GRN (15,0 %) et MAPT (9,2 %) présentaient des fréquences plus faibles. Les porteurs de la mutation génétique MAPT ont notamment développé une psychose à un âge plus précoce que les autres groupes génétiques. Les symptômes psychotiques les plus fréquents étaient les délires chez les porteurs de la mutation du gène C9orf72 et les hallucinations visuelles chez les porteurs de la mutation génétique GRN. Parmi les sous-types pathologiques, on a noté que 30 % des patients atteints d'une pathologie liée au gène FUS ont développé une psychose. Ce pourcentage était de 25,3 % chez des patients atteints d'une pathologie liée au gène TDP-43 et de 16,4 % chez des patients atteints d'une pathologie liée à la protéine tau. Dans le groupe TDP-43, une pathologie de sous-type B était le sous-type le plus souvent associé à une psychose. ***Conclusion :*** Notre étude systématique suggère donc une fréquence élevée de cas de psychose dans des sous-groupes spécifiques de patients atteints de DFT. D'autres études demeurent aussi nécessaires pour comprendre les fondements structurels et biologiques de la psychose dans la DFT.

Keywords: Psychosis; frontotemporal dementia; *C9orf72*; GRN; TDP-43; FUS

(Received 30 March 2023; final revisions submitted 21 June 2023; date of acceptance 24 June 2023)

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Cite this article: Chatterjee A, Hirsch-Reinshagen V, Scott I, Cashman N, and Hsiung G-YR. A Systematic Review of the Genetics and Pathology of Psychosis in Frontotemporal Dementia. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2023.248

Introduction

Frontotemporal dementia (FTD) is a neurodegenerative disease that presents with varying combinations of behavioral, language, and motor symptoms. Behavioral variant FTD (bvFTD) patients are diagnosed by the presence of apathy, disinhibition, loss of sympathy/empathy, stereotyped behavior, and hyperorality.[1] In addition, bvFTD patients may develop a range of neuropsychiatric symptoms including psychosis, depression, and anxiety.[2,3] Neuropsychiatric symptoms may precede the onset of cognitive deterioration and lead to diagnosis of a primary psychiatric disorder.[4] FTD patients with predominantly language or motor impairment (motor neuron disease or Parkinsonism) also develop behavioral and neuropsychiatric symptoms.

Due to these protean disease manifestations and the lack of *in vivo* biomarkers for FTD, it is likely that to date, the prevalence of neuropsychiatric symptoms has been difficult to correctly ascertain. Existing literature on this topic has also been conflicting. A previous review from 2009 found that 6% of reported FTD cases presented with psychosis, and a further 7.2% had psychotic symptoms during the disease course.[5] More recently, a systematic review from 2014 estimated the prevalence of psychosis in FTD at 10–15%.[6] However, the true prevalence may well be higher, with studies of patients carrying genetic mutations predisposing to FTD showing higher rates, in the range of 21–56% for those carrying the C9orf72 hexanucleotide repeat expansion.[7] Earlier reviews included cases that were not confirmed by autopsy, which likely impacts the accuracy of their predictions. FTD patients with psychosis are also more likely to receive psychiatric diagnoses initially, leading to a delay in the diagnosis of dementia and potential exclusion from some of these studies.[4,8] Hence, we believe that the true prevalence of psychotic symptoms in FTD remains uncertain.

In recent years, knowledge about the genetic and pathological underpinnings of FTD has rapidly expanded. We, therefore, decided to examine the characteristics of patients with a genetically and/or pathologically confirmed FTD diagnosis who developed psychosis in their clinical presentation and provide an updated review on the prevalence of psychotic symptoms in FTD. Unlike previous reviews, we only selected studies that reported a confirmed genetic or pathological etiology of FTD to improve accuracy of our estimates. This systematic review will also help us better understand the biological basis of psychosis in these patients and outline future research directions based on the identified knowledge gaps.

Method

To identify relevant articles, PubMed, MEDLINE, and Psycinfo databases were searched using the following keywords: "Frontotemporal dementia," "FTD," "Frontotemporal lobar degeneration," "Psychosis," "Genetics," "Pathology," "GRN," "MAPT," "C9orf72," "FUS," "TDP-43," and "Tau." The reference lists of articles of interest were also reviewed to obtain further relevant articles. The literature search returned 289 articles published up to December 2022. A further 27 articles were added through hand search and review of references. After removal of duplicates, the articles were screened with the following inclusion criteria: (1) articles that reported psychosis in FTD patients and (2) articles where genetic and/or pathological data were available for patients (Figure 1). Where studies were published by the same group, they were included unless a study was clearly a subset of a larger, more recent study. The time period of interest for psychosis was the early phase of the illness (i.e. within the first 3–4 years of symptom onset), so this time period was used preferentially when available. FTD had to be diagnosed based on either accepted clinical criteria or neuropathological examination. We also included studies with presymptomatic carriers of known causative mutations for FTD and *C9orf72* carriers who were diagnosed with amyotrophic lateral sclerosis (ALS). All variants of FTD were

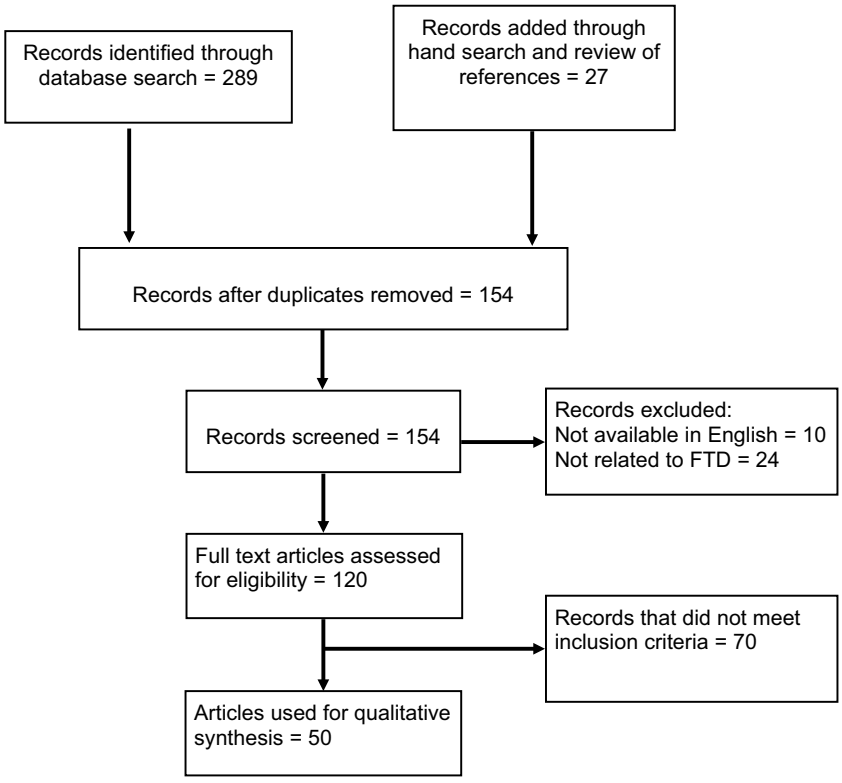

Figure 1: PRISMA flow diagram for systematic literature review.

https://doi.org/10.1017/cjn.2023.248 Published online by Cambridge University Press

included (behavioral variant FTD, non-fluent primary progressive aphasia (PPA), and semantic variant PPA). Articles that were not written in English were excluded. In articles with incomplete pathological or genetic data for all participants, we also excluded the cases where these data were unavailable.

From these articles, data on psychotic features (delusions and hallucinations), genetic results, and pathological correlations were extracted. The aggregate prevalence of psychosis in FTD patients was calculated from the articles included in our systematic review. The reported prevalence of psychosis in each genetic and pathological subgroup was also calculated. Individual patient data including age of onset, sex, types of psychotic symptoms, and presence of associated features (e.g. ALS) were also extracted wherever available.

Results

Fifty articles met the inclusion and exclusion criteria for this review (Table 1), which comprised 14 case reports, 16 case series, and 20 observational analytical studies (14 cohort studies, 5 case–control studies, and 1 cross-sectional study). Table 1 describes the study design, sample sizes, diagnostic criteria, and analytical methods used in these articles. Thirty-seven articles reported genetic data, 15 articles reported pathological data, and 13 studies reported some combination of genetic and pathological data for the included patients. The studies report a total of 1518 subjects with autopsy-confirmed FTD or carrying genetic mutations associated with FTD, out of which 368 patients (24.2%) developed psychosis (not including single case reports). There were 775 patients with a confirmed genetic mutation, the majority of these carrying the *C9orf72* hexanucleotide repeat expansion, and of these patients, 204 (26.3%) developed psychosis. We extracted available clinical characteristics of individual patients with psychosis, which are summarized in Supplementary Table 1 (N = 99).

Genetics

The genetic landscape of FTD has been gradually expanding. At least 30% of FTD patients have a causative genetic mutation, with the *C9orf72* hexanucleotide repeat expansion, *GRN* mutations, and *MAPT* mutations being the most common.[58,59] In addition, mutations in *VCP, CHMP2B, TIA1, TBK1, TARDBP, OPTN,* and *UBQLN2* are reported in small number of families all over the world.[52,59] Among the rarer genetic mutations, *UBQLN2* has been associated with psychosis in a recent case report.[52]

C9orf72

A hexanucleotide repeat expansion in the *C9orf72* gene, discovered in 2011, is the most frequent genetic cause of FTD and ALS in North America and Europe.[60] This repeat expansion may cause pathogenic effects through multiple mechanisms, including toxic gain-of-function and loss-of-function. According to the putative gain-of-function mechanism, *C9orf72* hexanucleotide repeats undergo transcription into repeat RNAs which sequestrate RNA binding proteins and are translated into dipeptide repeats, which form neuronal inclusions.[7,60] According to the putative loss-of-function mechanism, expansion of the hexanucleotide repeat in the promoter region of the *C9orf72* gene leads to lower protein levels of *C9orf72*, which impairs autophagy and lysosomal function.[60]

Our literature review revealed 29 articles that reported psychosis in association with the *C9orf72* mutation. Out of a total of 557 subjects with the *C9orf72* hexanucleotide repeat expansion, 175 subjects (31.4%) developed psychotic symptoms, making it the most common genetic mutation reported in association with psychosis and FTD. Compared to the total number of FTD patients with a confirmed genetic mutation with clinical psychosis we found in the literature (N = 204), *C9orf72* mutation carriers constituted the majority (86%), confirming the previously reported assertion that psychosis in the context of a family history of FTD is suggestive of *C9orf72* mutation.[28] A small study reported that a 10-base pair deletion adjacent to the *C9orf72* expansion may be protective against the development of psychosis.[44]

Patients with the *C9orf72* hexanucleotide repeat expansion demonstrate wildly different ages of onset and clinical presentations, including bvFTD, FTD-ALS, or ALS alone. The clinical characteristics of *C9orf72* carriers are summarized in Table 2. The mean age of onset of symptoms in *C9orf72* mutation carriers with psychosis was 55.7 years (Table 2). In addition to behavioral features of FTD, 27.0% of patients developed ALS and 23.6% of patients developed Parkinsonism. Among *C9orf72* mutation carriers, delusions were the most common psychotic feature. Patients reported bizarre delusions, hallucinations, or both.

Although most patients with psychosis developed cognitive and behavioral features suggestive of bvFTD, cognitive impairment may trail the onset of psychotic symptoms in *C9orf72* mutation carriers.[38] Patients with longstanding psychosis prior to the diagnosis of bvFTD have also been described.[3,32] In these situations, neuroimaging and genetic testing for the *C9orf72* mutation led to the final diagnosis. As patients with the *C9orf72* mutation may present with predominantly psychotic features, investigators examined cohorts of patients with a psychiatric diagnosis for the mutation. Screening of two cohorts of patients with schizophrenia and psychosis for *C9orf72* mutation did not reveal any mutation carriers, suggesting this is not a common cause of psychosis in the general population.[61] However, family members of *C9orf72* carriers are at increased risk of developing schizophrenia or psychosis[62], suggesting some pathogenic role of the *C9orf72* mutation in the development of psychosis in sporadic schizophrenia.

GRN

GRN encodes the progranulin protein, which is widely distributed throughout the body and has diverse functions, including neuronal differentiation and anti-inflammatory actions.[63] The *GRN* mutation was discovered as an etiology of autosomal dominant FTD in 2006.[64] Since then several pathogenic mutations have been described, which possibly cause neurodegeneration through a loss-of-function mechanism. Heterozygous mutations in *GRN* lead to haploinsufficiency and loss of functional progranulin protein.

Our literature search identified seven articles that reported psychotic symptoms associated with *GRN* mutations, which reported a combined prevalence of psychosis of 15.0% among *GRN* mutation carriers (N = 153). *GRN* mutations may be associated with bvFTD, a PPA syndrome, or a mixed phenotype.[59] The clinical characteristics of *GRN* carriers with psychosis are summarized in Table 2. The average age of onset of symptoms in *GRN* mutation carriers in our literature survey was 59.1 years. Visual hallucinations were the most common psychotic feature in *GRN* mutation carriers. In addition, cognitive deficits in the form of aphasia, apraxia and acalculia, and motor symptoms of Parkinsonism were present. Analysis of the Genetic FTD Initiative (GENFI) cohort revealed a 4% prevalence of hallucinations and a

https://doi.org/10.1017/cjn.2023.248 Published online by Cambridge University Press

Table 1: List of articles reviewed for literature synthesis (in order of publication year)

Author	Study design	N (psychosis/total no. of patients)	FTD diagnosis	Genetics	Pathology
Waddington et al, 1995[9]	Case report	1/1	Pathology		Pick's disease
Claassen et al, 2008[10]	Case series	2/2	Neary		FTLD-TDP
Le Ber et al, 2008[11]	Cohort study	8/32	Neary	*GRN*	
Tartaglia et al, 2008[12]	Case report	1/1	Pathology		FTLD-TDP
Moreno et al, 2009[13]	Case series	1/18	Neary	*GRN*	
Velakoulis et al, 2009[5]	Case series	5/17	Pathology		FTLD-TDP (4/10), FTLD-tau (0/5), FTLD-U (1/1), other (0/1)
Kremen et al, 2010[14]	Case report	1/1	Neary		Pick's disease
Loy et al, 2010[15]	Case report	1/1	Neary		FTLD-TDP
Momeni et al, 2010[16]	Case series	1/2	Lund and Manchester	*GRN*	
Urwin et al, 2010[17]	Case series	8/22	Neary		FTLD-FUS
Pearson et al, 2011*[18]	Case series	2/9	Pathology	*C9orf72*	
Rohrer et al, 2011[19]	Case series	1/5	Neary		FTLD-FUS
Boeve et al, 2012*[20]	Cohort study	10/20	FTDC	*C9orf72*	
Dobson Stone et al, 2012*[21]	Cohort study	5/9	FTDC	*C9orf72*	
Floris et al, 2012[22]	Case report	1/1	Genetics	*C9orf72*	
Hsiung et al, 2012*[23]	Case series	1/30	Pathology	*C9orf72*	
Khan et al, 2012[24]	Case report	1/1	Genetics	*MAPT*	
Mahoney et al, 2012*[25]	Case series	2/16	FTDC	*C9orf72*	
Sha et al, 2012[26]	Case–control study	5/25	FTDC	*C9orf72*	
Simón-Sánchez et al, 2012*[27]	Cohort study	2/42	Neary	*C9orf72*	
Snowden et al, 2012[28]	Case series	12/32	Neary	*C9orf72*	
Arosio et al, 2013[29]	Case report	1/1	Genetics	*GRN*	
Galimberti et al, 2013[30]	Case–control study	9/33	FTDC	*C9orf72*	
Kaivorinne et al, 2013*[31]	Case series	4/19	Neary	*C9orf72*	
Kertesz et al, 2013*[32]	Case series	5/8	Neary	*C9orf72*	
Landqvist Waldö et al, 2013*[33]	Case series	8/12	Neary	*C9orf72*	
Larner et al, 2013[34]	Case report	1/1	Genetics	*C9orf72*	
Mendez et al, 2013[35]	Case series	11/74	FTDC		FTLD-TDP (3/47)^ FTLD-tau (1/23)^ (first symptoms)
Devenney et al, 2014[36]	Case–control study	4/10	Genetics	*C9orf72*	
Gramaglia et al, 2014[37]	Case report	1/1	Genetics	*C9orf72*	
Sommerlad et al, 2014[38]	Case report	1/1	Genetics	*C9orf72*	
Landqvist Waldö et al, 2015[39]	Cohort study	31/97	Pathology		Pick's disease (2/9), FTLD-tau (4/12), CBD (1/8), PSP (0/1), FTLD-TDP (15/52), FTLD-FUS (3/5), unspecified (6/10)
Shinagawa et al, 2015*†40	Case series	4/17 (delusions)	Genetics, pathology	*C9orf72*	FTLD-TDP
Snowden et al, 2015*[41]	Cross-sectional study	25/74	Genetics	*C9orf72* (21/42), *GRN* (4/17), *MAPT* (0/15)	

(*Continued*)

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Table 1: (*Continued*)

Author	Study design	N (psychosis/total no. of patients)	FTD diagnosis	Genetics	Pathology
Solje et al, 2015[42]	Cohort study	18/36	Genetics	*C9orf72*	
Irwin et al, 2015[43]	Cohort study	2/21	Pathology		Pick's disease
Snowden et al, 2016[44]	Cohort study	20/36	Genetics	*C9orf72*	
Devenney et al, 2017[45]	Case control study	9/14	FTDC	*C9orf72*	
Suhonen et al, 2017[46]	Cohort study	7/29	FTDC	*C9orf72*	
Cheran et al, 2018[47]	Cohort study	1/12	Genetics	*MAPT*	
Giannoccaro et al, 2018*[48]	Case series	2/12	Genetics	*C9orf72*	
Sellami et al, 2018[49]	Cohort study	14/167	Genetics	*C9orf72* (7% hallucinations, 12% delusions; 7/60), *GRN* (4% hallucinations, 5% delusions; 4/75), *MAPT* (6% hallucinations, 9% delusions; 3/32)	
Payman et al, 2019[50]	Case report	1/1	Genetics	*C9orf72*	
Ferenczi et al, 2020[51]	Case report	1/1	Genetics	*MAPT*	
Raggi et al, 2020[52]	Case report	1/1	Genetics	*UBQLN2*	
Kawakami et al, 2021[53]	Cohort study	5/45 (delusions)	Pathology		FTLD-TDP (2/24), FTLD-tau (3/13), FTLD-FUS (0/8)
Burhan et al, 2021[54]	Case report	1/1	Genetics	*C9orf72*	
Devenney et al, 2021[55]	Case–control study	10/16	Genetics	*C9orf72*	
Naasan et al, 2021*+[56]	Cohort study	50/202	Pathology	*C9orf72* 8/30, *GRN* 5/9, *MAPT* 2/6	FTLD-TDP (26/69) FTLD-tau (24/133)
Devanand et al, 2022[57]	Cohort study	64/303 delusions^ 30/303 hallucinations^	Pathology		FTLD-TDP FTLD-tau FTLD-FUS
Total **Genetic** **Pathologic**		368/1518 204/775 183/805			TDP 56/221 Tau 37/225 FUS 12/40

FTDC=international consensus criteria for FTD.
*Study reporting a combination of genetic and pathologic data.
+Study reporting both genetic and pathologic data included in analysis.
^Numbers approximate; taken from graphical representations from the publication.

Table 2: Clinical characteristics of FTD patients with a genetic mutation and psychosis

Gene	Frequency of psychosis (%)	Average age of onset (Years)	Psychotic features	Behavioral features	Cognitive features	Motor features
C9orf72	31.4 (175/557)	55.7	Delusions> auditory/visual hallucinations	Disinhibition, apathy, agitation, perseveration	Aphasia, executive dysfunction	Motor neuron disease ± Parkinsonism
GRN	15.0 (23/153)	59.1	Visual> auditory hallucinations, delusions	Apathy, disinhibition, perseveration	Aphasia, apraxia, acalculia	Parkinsonism
MAPT	9.2 (6/65)	36.5	Delusions	Disinhibition	Aphasia	Parkinsonism

5% prevalence of delusions among *GRN* mutation carriers (N = 75).[49] Several mutations in the *GRN* gene were reported in patients with psychosis, including deletions (c.753–754del TG) and missense (c.1A > G) mutations. Le Ber et al reported a higher incidence of visual hallucinations among *GRN* mutation carriers.[11] They also reported a unique patient who was diagnosed with schizophrenia due to lack of cognitive impairment. Momeni et al also reported a family with the *GRN* mutation (c.675–676del CA) with history of early-onset psychosis, which was diagnosed as schizophrenia.[16] A genetic study of families with schizophrenia revealed a significant linkage with the genetic locus 17q21, which contains the *GRN* gene.[65]

https://doi.org/10.1017/cjn.2023.248 Published online by Cambridge University Press

MAPT

The *MAPT* gene encodes isoforms of the tau protein, which is involved in microtubule stabilization in neurons. *MAPT* was the first gene associated with the development of FTD, described by Hutton et al in 1998.[66] Since then several mutations in the *MAPT* gene have been described, which cause FTD through different mechanisms, including an altered 3R/4R tau ratio and abnormal tau phosphorylation.[67]

Our literature survey revealed six articles that reported psychosis in association with *MAPT* mutations. *MAPT* mutation carriers may present with clinical features of FTD, PPA, or an atypical Parkinsonian syndrome, such as corticobasal syndrome.[59] The articles reported 6 patients with psychotic symptoms out of a total of 65 patients with *MAPT* mutations (9.2%). The average age of onset of symptoms in patients with psychosis was 36.5 years, though the accuracy of this result is limited by small numbers. In *MAPT* mutation carriers, delusions were the prevalent psychotic feature, whereas frank hallucinations were rare.[56] Notably, the age of onset of *MAPT* mutation carriers with psychosis was younger than *C9orf72* or *GRN* mutation carriers, which has also been observed in previous publications.[68,69] Khan et al described a patient with longstanding psychosis prior to diagnosis of FTD.[24] A comparative study reported a lower frequency of psychotic features in *MAPT* mutation carriers (zero percent) compared to *GRN* (24% delusions and 6% hallucinations) and *C9orf72* (50% delusions and 21% hallucinations) mutation carriers.[41] Thirty-three percent of *MAPT* mutation carriers demonstrated Parkinsonism on neurologic examination.[44]

Pathology

The pathological cause of clinical FTD is frontotemporal lobar degeneration (FTLD) named after the pattern of brain atrophy identified on macroscopic examination of the brain. FTLD is subclassified based on the type of abnormal protein inclusions observed on histological examination. There are three main types of proteins that accumulate abnormally in FTLD: transactive response DNA-binding protein 43 kDa (TDP-43; FTLD-TDP), tau (FTLD-tau), and the FET family of RNA-binding proteins (FTLD-FET).[70] *C9orf72* and *GRN* mutations are associated with FTLD-TDP pathology, while *MAPT* mutations are associated with FTLD-tau pathology. The prevalence of psychosis is different for each pathological class; however, overall 22.7% of cases were found to have psychosis in this review. A single study was found that compared sporadic and genetic cases within pathological classes: it showed that patients with FTLD-TDP type B pathology with and without delusions had a similar percentage that tested positive for the *C9orf72* hexanucleotide repeat expansion.[56] This suggests that delusions were not necessarily predictive of the presence of this mutation.

FTLD-TDP

TDP-43 is a widely expressed RNA-binding protein that is predominantly localized in the nucleus of a cell. TDP-43 regulates metabolism of a wide variety of RNA species, which in turn regulate neuronal development and synaptic functions. Fifty percent of FTD patients demonstrate abnormal TDP-43 inclusions in the brain (FTLD-TDP).[67] Abnormal TDP-43 undergoes posttranslational modifications including phosphorylation and ubiquitination. The normal nuclear staining pattern of TDP-43 is also lost in FTD.

We retrieved 10 articles that reported psychosis in the context of FTLD-TDP pathology from the literature search. The studies reported a combined 223 patients with FTLD-TDP, including single case reports. Overall, 25.3% of patients with FTLD-TDP pathology were reported to have developed psychosis, most of these data taken from any point in the disease course. Among 61 patients with FTLD-TDP pathology and the *C9orf72* mutation, 12 patients (19.7%) developed psychosis.[21,23,25,33] Among 51 patients with FTLD-TDP pathology without the *C9orf72* mutation, 21 patients (41.2%) developed psychosis. In psychotic patients with FTLD-TDP pathology, delusions were slightly more common than hallucinations. A wide variety of delusions were reported, including delusion of pregnancy and bizarre somatoform delusions. Two studies reported a high prevalence of hallucinations in the range of 40–50%.[20,56] However, multiple studies specifically recruited patients with the *C9orf72* mutation[18,21,23,25,28], including one of these two studies. Therefore, the studies, which described patients with the *C9orf72* mutation, may have influenced the prevalence of psychosis in patients with FTLD-TDP pathology. Furthermore, several studies looked at psychosis at any stage of the disease course, so it could be that they have captured psychosis in late-stage disease, a feature of many neurodegenerative disorders.

Pathologically, the literature does not reveal a clear difference in general histological findings between patients with and without psychosis. Almost all studies reported degeneration of the frontotemporal cortex and variable involvement of the hippocampus, particularly the CA1 subsector.

FTLD-TDP pathology is heterogeneous in its cortical distribution and morphology of inclusions and has been further organized into several pathological subtypes named A to D.[70] We examined the reported prevalence among these subtypes in patients with psychosis. As some articles did not mention the subtypes specifically, VHR reviewed the pathological description and assigned subtypes according to the current classification. Within FTLD-TDP, subtype B (N = 21) was the most common subtype associated with psychosis in FTD patients, compared to four cases associated with subtype A (N = 4) and one case each with subtypes C and D.

FTLD-Tau

Approximately 40% of patients with FTD demonstrate abnormal tau pathology (FTLD-tau).[70] Tau is a phosphoprotein that promotes microtubule polymerization and stabilization of microtubules. Different isoforms of tau exist based on splicing of exon 10 of the tau-encoding *MAPT* gene. The isoforms are labeled 3R or 4R depending on the number of repeats of a 32 amino acid conserved sequence. FTLD-tau is a clinically and pathologically heterogenous group and comprises both 3R tauopathies (e.g., Pick's disease) and 4R tauopathies (e.g., corticobasal degeneration and progressive supranuclear palsy).

Nine articles described psychosis in association with FTLD-tau pathology in 227 patients, and in total, 16.4% with tau pathology developed psychosis. The average age of disease onset was 59.8 years. Most of the patients with psychosis were from a single study.[56] In this study, hallucinations were slightly more common than delusions, and over 50% of those with psychosis had both delusions and hallucinations. Delusions were less common when compared to patients with FTLD-TDP pathology. In addition, some of the patients with visual hallucinations had concomitant Lewy Body pathology, which may have been a contributing factor.[56] This was supported by logistic regression analysis in

https://doi.org/10.1017/cjn.2023.248 Published online by Cambridge University Press

another study, demonstrating an increased risk of delusions and hallucinations in patients with any concomitant Alzheimer or Lewy Body pathology.[57]

Pick's disease is characterized by argyrophilic, tau-immunoreactive pathological inclusions called Pick bodies, which are predominantly composed of 3R tau.[71] In this review, 5 articles reported 12 patients with psychosis associated with Pick's disease, or 17.9% of cases. The mean age of onset of symptoms in psychotic patients with Pick's disease was 56.3 years. A mixture of delusions and hallucinations were reported in these 12 patients, with the largest study reporting a slightly higher number with delusions than hallucinations, and a small proportion with both.[56] Hallucinations were often auditory.[9,43]

FTLD-FUS

In some patients with tau- and TDP-43-negative FTLD pathology, Fused in Sarcoma (FUS) was discovered to be the constituent of pathological inclusions.[17] FUS is a member of the FET family of RNA-binding proteins, which also include EWS RNA binding protein 1 (EWSR1) and TAF15.[70] FUS pathology is also observed in familial ALS, which is a result of mutations in the *FUS* gene. In contrast, FTD associated with FUS pathology is almost always sporadic.[72] FUS is involved in several steps of RNA metabolism, which include RNA granule formation, nucleo-cytoplasmic transport, and protein translation. FUS has a low-complexity domain that can form polymers and transition from soluble to insoluble states. This is a putative mechanism for neurodegeneration in FUS pathology.

Patients with FTLD-FUS pathology had a high overall prevalence of psychosis in our literature survey, though the proportion varied in individual studies likely due to small numbers. We retrieved five articles that reported psychosis in the context of FUS pathology.[17,19,39,53,57] The prevalence of psychosis was 30% among 40 patients reported in the retrieved articles. Patients with FTLD-FUS pathology had an earlier age of onset compared to sporadic bvFTD, which holds true for patients who develop psychosis as well. Although the ages of onset for all the patients were not available, one study reported three patients with FTLD-FUS and psychosis with an average age of onset 32.7 years.[39] It was also noted that patients with FTLD-FUS are more likely to receive a psychiatric diagnosis initially due to their early age of onset.

Discussion

We performed a systematic review to examine the relationship between the different genetic and pathological etiologies of FTD and the development of psychosis. Our review demonstrates interesting patterns that point toward biological mechanisms of psychosis. It also highlights areas that need further research to address the current imbalances in the literature. Earlier review articles demonstrated a variable prevalence of psychosis, for instance, Mendez et al observed a wide range in the prevalence of psychotic symptoms from 5 to 23 %,[35] while Shinagawa et al estimated the prevalence of psychosis in FTD as approximately 10%.[6] Our review with stricter inclusion criteria observed a higher prevalence of psychosis compared to previous reviews (24.2%). Furthermore, we observed that the prevalence of psychosis differed significantly among genetic and pathological groups, which is consistent with previous reports. We have also included new genetic mutations such as the *UBQLN2* mutation, in which an association between FTD and psychosis has also been found.

For context, the point prevalence of psychosis in the general population has been estimated at 3.9 per 1000 people (0.39%) and the lifetime prevalence 7.5 per 1000 (0.75%).[73] Hence, the prevalence of psychosis in FTD patients greatly exceeds this and cannot be explained by coexisting psychosis from other causes. The prevalence of psychosis in FTD found in our review is also similar to that seen in major depression (estimated at 28%) [74], but less than that observed in Alzheimer's disease (estimated at around 41% over the disease course).[75] It is also important to note that the psychotic episodes noted in these cases are a prominent and pervasive clinical feature and are not secondary to delirium.

The highest rate of psychosis in our review was found in patients carrying the C9orf72 hexanucleotide repeat expansion (31.4%). Since the discovery of the *C9orf72* mutation as a cause of familial FTD in 2011, the clinical phenotype has been extensively described in several centers. It is the most common mutation reported in FTD patients with psychosis, and the prevalence of psychosis in patients with the *C9orf72* mutation is much higher than those with *GRN* or *MAPT* mutations. However, in a longitudinal study of neuropsychiatric symptoms in sporadic and genetic FTD patients (GENFI), there was no significant difference in the prevalence of delusions and hallucinations among the genetic groups.[49] This study does include both symptomatic FTD patients and asymptomatic mutation carriers, which may have influenced the prevalence of psychotic symptoms. Longitudinal follow-up of the same cohort found that the prevalence of psychotic symptoms in *C9orf72* mutation carriers increases as their disease progresses.

We observed that FTD patients with psychosis associated with different mutations have slightly different clinical profiles. *C9orf72* mutation carriers developed prominent, bizarre delusions while *GRN* mutation carriers developed prominent visual hallucinations. *MAPT* mutation carriers predominantly reported delusions that became symptomatic at an early age. However, very few *MAPT* mutation carriers have been reported with psychosis. The predictive ability of the clinical features should be evaluated in larger prospective studies.

At present, it is unclear whether specific structural brain changes in the genetic groups lead to different susceptibility to psychosis. We speculate that each mutation has different effects on different brain networks. In a multi-center study on familial FTD, early changes in the temporal lobe were observed in *MAPT* mutation carriers, whereas the insula was affected early in *GRN* mutation carriers, while the thalamus was affected early in *C9orf72* mutation carriers.[49]

From a pathological perspective, patients with FTLD-TDP and FTLD-FUS pathology are more likely to develop psychosis compared to patients with FTLD-tau. Most of the FTLD-TDP cases with psychosis were associated with TDP-43 pathological subtype B. FTLD-FUS patients with psychosis have an early age of onset, which overlaps with primary psychiatric disorders. Among the different subtypes of FTLD-tau, Pick's disease patients are slightly more likely to develop psychosis. The reason for the difference in prevalence of psychosis among different pathological groups is not clearly understood. We speculate that this is a result of differential involvement of brain networks by different pathologies. It is noteworthy that both FTLD-TDP type B and FTLD-FUS are the FTLD types located on a spectrum with ALS. Relatives of patients with ALS have higher incidence of

https://doi.org/10.1017/cjn.2023.248 Published online by Cambridge University Press

neuropsychiatric conditions, including schizophrenia, which is only partially explained by the presence of *C9orf72* mutations.[76]

Our literature search did not reveal any particular pathological distribution associated with psychosis in FTD patients. While the exact neural substrate that leads to psychosis remains unknown, it has been noted that FTD patients with psychosis had higher pathological burden in the right hemisphere.[39] Another study of patients with ALS and FTD suggests that vulnerability in the thalamo-cortico-cerebellar networks may contribute to this symptom.[55] These intriguing observations require corroboration in a larger cohort of patients with all FTLD subtypes. More work is also required to evaluate treatment approaches to psychosis in FTD, which were not explored at any length in the articles reviewed.

The biological basis of psychosis in FTLD could have several causes, including a common localization of FTD-associated neurodegeneration and primary psychiatric disease without apparent neurodegeneration. A provocative recent publication indicated that Disrupted In Schizophrenia-1 (DISC1) protein can coaggregate with TDP-43 inclusions in human FTLD-TDP-43 and in mouse models of TDP-43 FTD.[77] In the mouse neuroblastoma cell line N2a, knockdown of DISC1 was found to depress activity-dependent dendritic local translation through impairment of protein translation initiation and, in turn, reduced synaptic protein expression, suggesting a link between TDP-43/DISC1 coaggregation and synaptic dysfunction underpinning psychosis. However, there is no association of schizophrenia and DISC1 variants on genome-wide association studies[78], despite the original observation that a DISC1 balanced translocation was linked to psychosis in a Scottish family.[79] The coaggregation of DISC1 with TDP-43, as well as other proteins implicated in FTLD, will require further neuropathological and biological investigations to better understand the implications.

Our current review has several limitations. One important factor is the time course of disease. While many of the genetic studies evaluated the prevalence of psychosis early in the disease course or in the presymptomatic stage, the pathological studies were often retrospective and recorded psychosis at any time throughout the patient's illness. The prevalence of psychosis tends to rise with increased duration of illness, which was well illustrated across all genetic groups in a recent article from the GENFI group.[80] The variable timing of clinical data collection is a significant limitation in this study, which may also explain some of the variability seen in earlier review articles.

Further limitations include the fact that for some of the subgroups analzsed, the absolute number of patients was small and may have been significantly influenced by findings from a single study. The techniques used for gathering data about the presence of psychosis are also variable and include scoring systems such as the Neuropsychiatric Inventory, structured clinical interviews, caregiver reports, and retrospective review of clinical records. This is also likely a source of the heterogeneity found between studies. Finally, our review found a large number of studies reporting psychosis in *C9orf72* mutation carriers, which may artificially exaggerate the prevalence of psychosis in FTD patients as a whole.

In conclusion, our systematic review shows a high prevalence of psychosis among genetic and pathologically confirmed cases of FTD. The *C9orf72* mutation and its associated TDP-43 pathology as well as FUS pathology have the strongest association with psychosis. However, the current literature may be skewed toward *C9orf72* mutation due to its more recent discovery and therefore possibly more comprehensive phenotyping of psychiatric features. Further prospective studies including sporadic and familial cases with neuropathological confirmation will be required to estimate the true risk of psychosis in all FTD patients.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2023.248.

Acknowledgments. Dr. Hirsch-Reinshagen acknowledges support from the UBC clinician-investigator program.

Dr. Scott acknowledges support from the VJ Chapman fellowship grant from the New Zealand Neurological Foundation.

Dr. Hsiung acknowledges support from the Ralph Fisher Professorship in dementia research from the Alzheimer Society of British Columbia.

Authors' contribution. AC and GYRH conceived and performed analysis on this study and drafted the initial manuscript. VHR and NC provided input to the study design, and critical review and revisions on the manuscript. IS updated and revised the manuscript with recent data.

Competing interests. Drs. Chatterjee, Hirsch-Reinshagen, and Scott have nothing to disclose.

Dr. Cashman discloses that he has received grants or contracts from CIHR, Weston Brain Institute, ProMIS Neurosciences, and is on the board of directors of ProMIS Neurosciences, and owns stock and options in ProMIS Neuroscience.

Dr. Hsiung discloses that he has received grants or contracts from CIHR, NIA/NIH, has been a clinical trials investigator supported by Biogen, Cassava, and Lilly, has participated in expert advisory committee supported by Biogen, Roche, and Novo Nordisk, and is the current president of C5R (Consortium of Canadian Centres for Clinical Cognitive Research).

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