Psychiatric Presentations of *C9orf72* Mutation: What Are the Diagnostic Implications for Clinicians?

Simon Ducharme, M.D., M.Sc., F.R.C.P.(C), Sepideh Bajestan, M.D., Ph.D., Bradford C. Dickerson, M.D., Valerie Voon, M.D., Ph.D.

The *C9orf72* mutation was identified as the most frequent genetic cause of frontotemporal dementia (FTD). In light of multiple reports of predominant psychiatric presentations of FTD secondary to *C9orf72* mutation, the American Neuropsychiatric Association Committee on Research reviewed all studies on psychiatric aspects of this mutation to identify clinically relevant features for diagnosis. The most common psychiatric presentation is psychosis (21%−56%), with delusions, and/or multimodal hallucinations. Other presentations include late-onset mania and depression with cognitive impairment or catatonia. However, the frequency of *C9orf72* mutations is low in typical schizophrenia or bipolar disorders (<0.1%). The authors provide clinical guidance on diagnosis and genetic testing.

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It has been known for many years that frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) share some common genetic basis. Indeed, many families demonstrate autosomal-dominant inheritance patterns of FTD, ALS, and/or FTD-ALS complex. The causative mutation was identified simultaneously by two groups in 2011 as being a hexanucleotide repeat on chromosome 9, the *C9orf72* mutation.[1,2] This major discovery has generated substantial interest in the scientific community, with over 700 publications on this topic since the initial reports.

The prevalence of FTD is 15–22 per 100,000, with around 20% of cases secondary to autosomal dominant mutations.[3] The *C9orf72* mutation was found to probably be the most common genetic form of FTD, being present in 7%−12% of subjects.[4] Of significant interest, pathogenic repeat expansion has been identified in 2%−5% of apparently sporadic FTD cases,[5] i.e., in patients without family history suggestive of dominant inheritance.

The most common clinical presentations of *C9orf72* mutations are behavioral variant FTD (bvFTD), ALS, or a combination of both (FTD-ALS).[4] The bvFTD syndrome presents with variable combinations of behavioral symptoms, including apathy, disinhibition, loss of empathy, stereotyped/repetitive behavior, and hyperorality.[6] Cognitive impairment in bvFTD due to *C9orf72* mutations includes the typical deficits in social cognition and executive function but can also involve memory disturbances and parietal lobe deficits.[4,7] ALS is often associated with early behavioral and cognitive changes, even when not meeting criteria for FTD-ALS.[8] In ALS due to *C9orf72* mutations, the phenotype is clinically indistinguishable from idiopathic ALS at the motor level, but with probably higher rates of behavioral and cognitive disturbances.[4,9] The language variants of FTD spectrum diseases, referred to as primary progressive aphasias (PPA), can also be associated with behavioral and psychiatric disturbances, although to a lesser degree than bvFTD.[10] PPAs are a more uncommon presentation of *C9orf72*, with most reported cases being nonfluent or semantic variants.[7,11]

Of particular interest to the neuropsychiatric community, phenotypic characterization of clinical cohorts of patients with *C9orf72* have hinted toward an unusually high frequency of late-onset psychotic disorders as the initial presentation, sometimes many years prior to the onset of more typical FTD or ALS symptoms.[7,12] Subsequent reports have described a wide variety of presentations, such as mania and bipolar disorder, major depressive episodes with catatonic features, and obsessive-compulsive disorder. These studies raise concrete and important questions for clinical practice across multiple settings, particularly in adult psychiatry: 1) How common are these presentations? 2) Could some cases of late-onset psychosis be explained by *C9orf72* mutation? 3) Who should get genetic testing? Although there are still no disease-modifying treatments for FTD or ALS secondary to *C9orf72* mutations, identifying the mutation in patients has major implications for prognosis and family counseling.

As an attempt to resolve these important clinical issues, the Committee on Research of the American Neuropsychiatric Association (ANPA CoR) has decided to undertake a comprehensive review of predominant psychiatric

presentations of *C9orf72* mutations to shed light on this topic and suggest clinical recommendations to clinicians.

BASIC GENETICS

The *GGGGCC* (also called *G4C2*) repeat expansion is located in chromosome 9 open reading frame 72 (*C9orf72*) gene on the short arm of the chromosome. Although the exact function remains uncertain, studies have identified possible protein isoforms that are thought to contribute to the regulation of endosomal trafficking.[13] The *C9orf72* mutation has three transcription variants, depending on whether the hexanucleotide repeat expansion is located in the promoter region (variant 1) or in intron 1 (variants 2 and 3).[1] In healthy controls, the normal hexanucleotide repeat size is usually up to 10 and on rare occasions up to 30 repeats.[1, 14–16] Repeat sizes between 20 and several hundred have been identified in both healthy controls and patients.[4,15,17–22] Repeat lengths of more than several hundred are very likely to be pathogenic for ALS or FTD.[1,4,23] The exact pathogenic number of repetition is difficult to determine for many reasons. The hexanucleotide repeat expansion in somatic tissues and blood is usually unstable (that is, within an individual, various organ tissues may exhibit different repeat lengths). Therefore, intermediate repeat lengths in blood or somatic tissue might be present in an individual with pathogenic repeat length expansion in the brain.[14] In addition, there is no direct connection between the number of repeats and the clinical phenotype severity, and data are not consistent on whether there is an association with the age of onset of the disease.[15] Furthermore, the mutation has been identified in up to 0.15% of the healthy population in the United Kingdom.[15]

The familial cases demonstrate autosomal dominant pattern of inheritance. Age of onset, even within a family, varies widely. Some kindred appear to exhibit an anticipation-like phenomenon.[24] However, studying anticipation in affected families has been challenging, given that the repeat expansion is unstable and variable in size across the cells. Cases of incomplete penetrance have also been reported.[25]

FTD cases secondary to *C9orf72* mutations are associated with TAR DNA binding proteins (TDP-43) pathology types A and B, in addition to specific p62/SQSTM1-positive neuronal cytoplasmic inclusions containing dipeptide repeat (DPR) proteins from the translation of the abnormal gene.[4,26] The precise pathogenic mechanism of *C9orf72* hexanucleotide repeat expansion remains uncertain. Potential explanations include loss of function, gain of function, or a combination of both.

1. Loss-of-function mechanisms: The *C9orf72* protein has been shown to regulate endosomal trafficking and autophagia in neuronal cell lines, primary cortical neurons, and human spinal cord motor neurons.[13] *C9orf72* is also homologous to DENN proteins (differentially expressed in normal and neoplasia proteins), which regulate membrane trafficking function by activating RAB GTPases.[20,27] The observation of lower levels of normal *C9orf72* transcript variants in the brain, spinal cord, and blood in patients with *C9orf72* expansions compared with healthy controls or patients without the *C9orf72* expansions underlies the hypothesized loss-of-function mechanism.[1,23,28–30]
2. Gain-of-function mechanisms: The toxic products of *C9orf72* hexanucleotide repeat expansion's transcription (toxic RNA repeat structures) and translation (toxic DPR proteins) are suggested as the main players in the gain-of-function mechanisms. The hexanucleotide repeat expansion's toxic RNAs have been found in the regions affected by the disease[31–34] and are believed to bind and sequester RNA-binding proteins.[28,35–42] However, the role of RNA-binding protein sequestration in disease pathogenesis is yet to be illuminated.

The unconventional repeat-associated non-ATG translation of the *C9orf72* hexanucleotide repeat expansion results in the formation of DPR proteins.[43] DPRs have been shown to be toxic in a range of model organisms[33,39,44] and cell lines.[34] DPRs were also localized in the affected brain regions of FTD-ALS patients.[45,46] The dysregulation of nucleocytoplasmic transport and the consequent neurodegeneration are thought to be the main pathogenic mechanisms of PDR proteins' toxicity.[13,27]

In summary, past studies suggest that *C9orf72* expansion results in both loss- and gain-of-function mechanisms, but further studies are warranted to elucidate the relative contribution of these mechanisms and the molecular pathways that lead to neurodegeneration.

METHODS

The goal of this project was to review the literature related to psychiatric presentations of *C9orf72* and the frequency of mutations in primary psychiatric disorders, with the ultimate objective being to provide concrete guidance to clinicians on how to approach this clinical problem. The main focus of the review was to identify key clinical features to improve diagnostic recognition in clinical practice, including when genetic testing should be obtained or not. Management and treatment aspects were reviewed in the identified articles, but this was a secondary objective given the very limited literature on the topic.

A PubMed search was conducted including all English language articles up to July 2016. A keyword strategy was used including the following search terms:

"*C9orf72*" AND
- "Psychosis" OR "Schizophrenia"
- "Bipolar Disorder" OR "Mania"
- "Depression"
- "Anxiety" OR "Obsessive-Compulsive Disorder (OCD)"
- "Catatonia"
- "Psychiatry"

A complementary Google Scholar search with the terms "C9orf72" AND "Psychiatry" was performed to identify any missing articles (one additional article was identified). All abstracts obtained by the keyword search were reviewed by the primary investigator (S.D.) to exclude articles that were not relevant to one of the two objectives and to delete duplications. A total of 43 articles were identified with the following breakdown: schizophrenia/psychosis (N=25), bipolar disorder/mania (N=4), depression (N=2), anxiety/OCD (N=2), catatonia (N=1), and psychiatry (N=9 articles not identified by single-symptom search terms). Articles were divided into two categories according to the objectives: 1) articles related to the psychiatric presentations of *C9orf72* mutations and 2) articles related to the prevalence of *C9orf72* mutations in cohorts of patients with primary psychiatric disorders. All articles were systematically reviewed by the coauthors to produce this report. Results were initially presented at the 27th Annual Meeting of the American Neuropsychiatric Association in San Diego (March 2016). The level of evidence varied depending on subtopics. There were good-quality case-control and epidemiological studies for psychosis (section 4.1) and for the prevalence of *C9orf72* mutations in primary psychiatric disorders (section 5). The evidence was of lower quality for other psychiatric symptoms, consisting either of small case series or single case reports.

CLINICAL PRESENTATIONS

Psychosis

The frequency of psychotic symptoms (delusions and/or hallucinations) in sporadic FTD is relatively low, with a recent estimate of a 10% prevalence.[47] Reports of increased frequency of psychotic symptoms in the early stages of FTD secondary to *C9orf72* mutations emerged from multiple sources in 2012,[7,12] one year after the discovery of the mutation. A total of 10 studies documenting the prevalence of psychosis in cohorts of patients with FTD-related *C9orf72* mutations have been identified (Table 1). A few case reports were also identified.[48–54] These studies have consistently reported a marked increased frequency of psychosis at the onset of FTD or preceding more classical FTD symptoms in patients with *C9orf72* mutations.[7,12,55–61] These studies showed a prevalence of psychotic symptoms in the range of 21% to 56%. Although published studies strongly support this increased rate of psychosis, there are unexplained geographic discrepancies in prevalence, including much lower rates of psychiatric disturbances recently reported by a German consortium at the last International Conference on Frontotemporal Dementia.[62]

Other than the overall increased prevalence of psychosis, a few additional key features emerged from these studies. First psychotic symptoms can include both delusions and hallucinations in all sensory modalities, together or separated. Second, there is a high frequency of somatic delusions (e.g., foreign object in body, pregnancy) in addition to unexplainable somatic symptoms or preoccupations (e.g., pain) that do not reach delusional intensity.[7,48,51,59,61] Delusion subtypes that have been reported also include persecution, jealousy, grandiose, and mystical/religious.[51] We are not aware of any study that has directly compared the nature of delusions between primary psychotic disorders or bipolar disorder versus FTD due to *C9orf72*, but other than a possibly higher prevalence of somatic delusions found in some[7] but not all[51] studies, the content of delusions appears to be relatively similar between these disorders. Third, psychotic symptoms often precede the appearance of more typical FTD features by 1–5 years.[51,56] Finally, although this is more anecdotal, reports consistently describe poor response and adverse reactions to antipsychotic medications.[59,63]

These studies on psychotic symptoms also highlighted important features of the atypical aspects of FTD secondary to *C9orf72* mutations. More than a third of cases did not have a family history of FTD-ALS; therefore, in clinical practice these cases would be considered as sporadic FTD.[7,57] In addition, multiple subjects did not show significant atrophy on MRI in the initial assessments.[57,56] When atrophy is present, the pattern is not restricted to frontotemporal areas, with frequent involvement of parietal regions, cerebellum, and thalamus.[64] In the absence of those typical neuroimaging findings, one study showed that 62% did not meet research criteria for probable bvFTD.[6,55] Solje et al.[60] similarly showed that among 36 patients with some bvFTD symptoms due to a *C9orf72* mutation, 19% did not meet the full research criteria for possible bvFTD and 36% did not meet criteria for probable bvFTD. In addition, 17.6% of subjects had a normal FDG-PET or SPECT,[60] which are thought to be more sensitive for bvFTD diagnosis than MRI. The lower sensitivity of diagnostic criteria in this population could also be in part related to decreased frequency of apathy (the most common symptom in sporadic bvFTD)[65] and higher emotional warmth at the onset.[56,61] In addition, patients with *C9orf72* have a higher rate of family psychiatric history,[55] a factor that has been shown to bias clinicians toward missing FTD diagnoses.[66] Factoring all these aspects, clinicians need to have a high index of suspicion in patients with late-onset psychotic disorders in order to identify potential *C9orf72* cases, because they cannot rely solely on the absence of the usual bvFTD clinical features described in the diagnostic criteria to exclude this possibility.

Mania and Bipolar Disorder

In 2013, Floris et al. published a case report of a patient who presented with bipolar I disorder at age 42 with both episodes of mania and hypomania.[67] He had a family history of bipolar disorder in one uncle, and his symptoms responded well to lithium. At age 64 he presented with more classical bvFTD symptoms (repetitive behavior, disinhibition, attentional and executive function deficits), delusions, and mild Parkinsonism. Although many of these symptoms could be

TABLE 1. Studies on the Prevalence of Psychotic Symptoms in *C9orf72*-Related Frontotemporal Dementia[a]

Study	Population	Method	Outcomes Related to Psychosis
Dobson-Stone et al.[12]	89 clinical FTD and 22 proven pathological TDP-43 (total 108 subjects) screened for *C9orf72* (15.7% positive)	Cross-sectional comparative group study comparing frequency of psychosis in *C9orf72* vs sporadic cases	55.6% (5/9) prevalence of psychosis in clinical FTD due to *C9orf72* vs 13.9% (11/79) in sporadic clinical cases No data on psychosis in the pathological cohort
Snowden et al.[7]	398 FTLD cohort screened for *C9orf72* (8% positive)	Cross-sectional comparative group study comparing frequency of psychosis in *C9orf72* vs sporadic cases	38% of *C9orf72* subjects presented with psychosis at the onset, in addition to 28% of bizarre behavior and paranoid ideations Psychotic symptoms included somatic delusions and visual/auditory hallucinations Increased frequency of complex compulsions in *C9orf72* cases
Galimberti et al.[57]	651 FTLD spectrum screened for *C9orf72* (6% positive) No cases found in 21 CBS and 31 PSP	Cross-sectional comparative group study comparing frequency of psychosis in *C9orf72* vs sporadic cases	30.3% (10/33) of *C9orf72* with late-onset psychosis at onset vs 8.1% (3/37) Symptoms included hallucinations, delusions, and aggression due to hypomania 12/29 *C9orf72* with atypical imaging including two cases without atrophy
Kaivorinne et al.[56]	73 FTLD cases screened for *C9orf72* (29% positive)	Cross-sectional comparative group study comparing frequency of psychosis in *C9orf72* vs sporadic cases	21% of *C9orf72* with psychosis at presentation vs 10% of sporadic cases (difference not statistically significant) Psychosis started one to five years prior to typical bvFTD features
Landqvist et al.[59]	Study of 12 bvFTD due to *C9orf72* from one family	Case series	8/12 with psychotic symptoms (hallucinations and delusions)[b] 7/12 with unexplained somatic complaints (pain most common) Four suicidal ideations All subjects had adverse reactions to antipsychotics (Parkinsonism)
Devenney et al.[55]	114 FTD screened for *C9orf72* (34% of bvFTD positive and 17% of FTD-ALS positive)	Cross-sectional comparative group study of 10 *C9orf72* positive cases vs 19 matched sporadic FTD	Higher frequency of psychosis in *C9orf72* (40%), significant for delusions and hallucinations Family history of psychiatric disorders higher in *C9orf72* cases vs sporadic cases (40% vs 5%) Apathy less common at the onset of *C9orf72* cases
Kertesz et al.[58]	61 FTD screened for *C9orf72* mutation (11.5%)	Cross-sectional comparative group study of eight *C9orf72* positive cases vs 44 sporadic cases Detailed case description	3/8 *C9orf72* cases (37.5%) with predominant psychotic symptoms at onset One case with psychosis onset 30 years prior to bvFTD Prevalence of hallucinations higher in *C9orf72* vs sporadic FTD (50% vs 5%). Prevalence of delusions in higher in *C9orf72* versus sporadic FTD (25 versus 18%).
Solje et al.[60]	36 *C9orf72* cases (32 bvFTD, 4 FTD-ALS	Chart review	Psychiatric symptoms other than bvFTD present in 61.1% 30.6% with psychotic symptoms only and 19.4% with both psychotic and mood symptoms

continued

TABLE 1, *continued*

Study	Population	Method	Outcomes Related to Psychosis
Shinagawa et al.[51]	17 cases with pathologically proven FTLD due to *C9orf72*	Chart review	4/17 (23.5%) with delusions but no mention of hallucinations[c] Greater precuneus atrophy in subjects with delusions Parkinsonism in all subjects with delusions
Snowden et al.[61]	74 genetic FTD (42 *C9orf72*, 15 MAPT, 17 GRN)	Cross-sectional comparative group study	Higher prevalence of psychosis in *C9orf72* (50%) than in GRN (24%) and MAPT (0%) 21% of somatic delusions in C9orf72, none in the other groups *C9orf72* associated with increased warmth at onset in comparison with other two groups

[a] ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; GRN, granulin; MAPT, microtubule associated protein tau; PSP, primary supranuclear palsy; TDP-43, TAR DNA-binding proteins.
[b] This study was not included in the range of prevalence, given that it was limited to one family.
[c] This study was not included in the range of prevalence because of the lack of data on hallucinations and disorganized behavior.

explained by a manic episode, MRI demonstrated frontal atrophy, and a genetic test showed more than 70 repeats of the *C9orf72* region, confirming a diagnosis of definite bvFTD. While this could have been coincidental, other reports have described relatively similar situations. One case in the Galimberti et al.[57] study presented with agitation/mania. In addition, cases of *C9orf72* have been identified in cohorts of typical bipolar disorder patients (see the section on the prevalence of *C9orf72* mutations in primary psychiatric disorders).[24,68] This includes a 35-year-old patient with typical lithium-responsive bipolar I disorder whose father suffered from bipolar I disorder at age 62, followed by bvFTD at 66.[24] A *C9orf72* mutation was also found in a 37-year-old male with major depressive, mixed and manic episodes who also responded to lithium. Although the numbers remain small, these reports suggest that late-onset bipolar I disorder (particularly manic episodes) can rarely be the initial clinical manifestation of *C9orf72* mutations and that these episodes tend to be lithium responsive.

Major Depressive Disorder (MDD)

MDD is the most common psychiatric diagnosis preceding the recognition of bvFTD[66]; however, there are few reports related to *C9orf72* mutations. One study showed a 30% rate of mood/affective symptoms in mutation cases, but with little information as to what was included in this classification.[60] One case report described a man who suffered a traumatic brain injury at age 40 with permanent cognitive and judgment deficits.[69] At age 66 he developed depressive symptoms and made a suicide attempt in the context of grief. The course was complicated by retarded catatonia that responded to antidepressants, aripiprazole augmentation, lorazepam, and ECT. This was followed by a relapse 6 months later with added impulsivity, restlessness, repetitive behaviors, and REM sleep behavior disorder with progressive deterioration. A brain MRI showed frontal atrophy, and a *C9orf72* expansion was confirmed. His mother had suffered from an unidentified progressive neuropsychiatric syndrome over a 20-year period. One patient presented at age 46 with an agitated depression that evolved into bvFTD with significant psychotic symptoms and intolerance to antipsychotics.[63] At autopsy she had extensive DPR aggregates but minimal TDP-43. Of note, her son, who suffered from intellectual disability, died at age 26 of unrelated causes but was found to be a carrier and have DPR aggregates without TDP-43 at autopsy.

Using a postmortem approach, Bieniek et al.[70] tested for the mutation in 31 brains without macroscopic atrophy in which the clinical diagnosis had been dementia (N=3), depression (N=6), or both, which they referred to as "depressive pseudodementia" (N=22). Of those 22 "pseudodementia" cases, two were found to be positive for the *C9orf72* mutation and had C9RANT neuronal inclusions, with the most severe deposits in the cerebellum. In one patient, major depression started at age 52, and over time the patient developed unexplained toe numbness (at age 57), drug-induced parkinsonism, and catatonia (at age 65) and died at age 66. His brain MRI was normal at age 61 but showed mild atrophy at 65. His father suffered from MDD and Parkinsonism. The other case had MDD at age 66, followed by attentional and short-term recall deficits that were clinically thought to be secondary to Alzheimer's disease.

Anxiety and OCD

Very few studies were found on the topic of anxiety. One case series of 19 patients with *C9orf72* mutations reported a 33% rate of anxiety as part of the initial presentation, but without specifying the nature of this anxiety.[11] We also identified two case reports of OCD as the initial presentation of bvFTD due to *C9orf72* mutations,[71,72] which is also a known presentation of sporadic bvFTD.[73]

TABLE 2. Prevalence of *C9orf72* Mutations in Cohorts of Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder[a]

Study	Cohort	Country	Threshold	Prevalence of *C9orf72* Mutations
Huey et al.[77]	192 subjects with schizophrenia	United States	Repeat-primed PCR to identify "sawtooth pattern with a 6 bp periodicity"	0/192
Meisler et al.[24]	89 BD enriched for early onset and neurocognitive abnormalities	United States	PCR screen followed by Southern blot	1/89 with approximately 2,600 repeats Father had late-onset BD evolving into FTD
Fahey et al.[79]	1,271 subjects including SZ (N=742); BD (N=261); SZA (N=162); MDD/delusional (N=106); 1243 case controls	Ireland	>30 repeats	0/1,243 with >30 repeats 7 subjects with >22 repeat (two cases; five controls)
Floris et al.[83]	206 BD	Sardinia	>30 repeats	0/206
Galimberti et al.[82]	297 subjects with SZ	Germany and Italy	>40 repeats	2/297 (0.67%) 1 subject with onset at 33 years old, one with onset at 44-years old
Galimberti et al.[68]	306 BD	Germany and Italy	>40	1/206 (0.5%); 0/100
Yoshino et al.[78]	466 subjects with SZ	Japan	>40 repeats	0/466
Solje et al.[81]	130 subjects with psychotic disorders (majority SZ)	Finland	>40 repeats	0/130
Watson et al.[80]	739 subjects including SZ (N=422), SZA (N=274), psychosis not otherwise specified (N=1), 37 controls, and five unaffected relatives	United States	N/A	4/739 from two families 3/697 psychotic disorder (0.4%) with primary psychotic disorder One subject with childhood-onset treatment refractory SZ

[a] BD, bipolar disorder; FTD, frontotemporal dementia; MDD, major depressive disorder; PCR, polymerase chain reaction; SZ, schizophrenia; SZA, schizoaffective disorder.

Catatonia

Catatonia has been previously reported in patients suffering from bvFTD.[74] Two cases were found in patients with *C9orf72* mutations, both described above.[69,70]

Suicide

Patients suffering from bvFTD are usually unaware of the severity of their deficits; therefore, suicide attempts are rare. We identified one case report of a patient with bvFTD due to *C9orf72* with minimal cognitive deficits who was first brought to clinical attention after a serious suicide attempt.[75] A patient described in the MDD section also attempted suicide as part of a depressive syndrome.[69] Suicidal ideations were also reported in multiple members of a Swedish family.[59] However, there are insufficient data to conclude whether the frequency of suicide attempt is higher in patients with the mutation than in sporadic cases. Of note, a recent study did not find any *C9orf72* mutation in a postmortem cohort of 109 victims of suicide (without FTD) in Finland.[76]

PREVALENCE OF *C9ORF72* MUTATIONS IN PRIMARY PSYCHIATRIC DISORDERS

In the context of the relatively high prevalence of psychiatric symptoms at the onset of *C9orf72* mutations and the frequently atypical nature of those patients, various groups have investigated whether the mutation could be the cause of some cases of patients with primary psychiatric disorders. We identified studies that screened large clinical populations for the mutation in both schizophrenia/schizoaffective disorder and bipolar disorder but not in other major psychiatric disorders.

We identified six studies in schizophrenia and schizoaffective disorders spanning North America, Europe, and Asia (Table 2).[77–82] Four of those studies did not identify a single case in a total of 1410 subjects. One study from Germany and Italy identified two cases out of 297 patients.[82] One patient had paranoid and grandiose ideations with a thought disorder starting at age 33. There was a family history of a sister with dementia and Parkinsonism and unspecified dementia in the mother. The other patient had onset of paranoid ideations and mood symptoms at age 44 (which is atypically late for schizophrenia), with a family history of schizophrenia in his mother. A recent American study found three positive cases out of 697, including one patient with treatment-refractory childhood-onset schizophrenia.[86] Pulling together all six studies, the prevalence of *C9orf72* mutation is estimated at below 0.1% in patients with typical schizophrenia or schizoaffective disorders.

A total of four American and European studies have investigated the frequency of the mutation in large cohorts of patients with bipolar disorder (Table 2).[24,68,79,83] Two cases were identified out of 862 patients. One of those patients had a family history of a father with late- onset

bipolar disorder progressing to FTD (described above).[68] This amounts to a prevalence of approximately 0.1%, which is similar to the rate of the mutation found in healthy controls in one study.[15]

MECHANISTIC HYPOTHESES

The exact function of the *C9orf72* gene remains to be elucidated; therefore, the mechanism by which the mutation increases the prevalence of psychiatric prodromes in FTD is unknown. However, there are a few interesting hypotheses. First, the atrophy pattern is more atypical in patients with *C9orf72* mutation compared with sporadic cases, with more severe involvement of the cerebellum and the thalamus, two structures that could contribute to the different clinical presentations.[4,64] In addition, preliminary results from the GENFI study have suggested that volume loss in the insula, parietal lobe, thalamus, and cerebellum could start more than 10 years prior to bvFTD clinical symptoms.[84] The cerebellum has a key role in modulating thoughts, affect, and behavior[85]; therefore, involvement of this structure could contribute to psychiatric phenotypes. Of interest, one study found a higher expression of the *C9orf72* gene in the cerebellum of patients suffering from schizophrenia.[86] One study reported a correlation between the degree of precuneus atrophy and the presence of delusions among patients with *C9orf72* mutation.[51] A small study has also shown potential differences in network connectivity in patients with *C9orf72* compared with sporadic FTD. Both groups showed an increase in default mode network connectivity, but of lesser magnitude in *C9orf72* compared with sporadic cases,[87] which could theoretically have a link to the more preserved emotional warmth observed in the early stages.[61] There is also one study that reported a link between a 10-pair deletion prior to the *C9orf72* expansion and the expression of psychotic symptoms, but this finding has not yet been replicated.[88]

While this is not a mechanistic explanation, Downey et al.[89] have run a series of experiments of body schema perception tasks in patients with the mutation compared with sporadic FTD and controls.[95] The idea to conduct these tasks came from the high frequency of somatic complaints and even somatic delusions in these patients. Results demonstrated altered body schema processing in patients with the mutation in various tasks such as two-point discrimination, body part illusions, and self- versus non-self-differentiation.

CLINICAL IMPLICATIONS

This review identified a few key findings as they pertain to the psychiatric presentations of *C9orf72* mutations. First, among the psychiatric prodromes, psychotic symptoms seem to be the most common, including various combinations of delusions or overinvested ideas and multimodal hallucinations. There is a high prevalence of unexplained somatic preoccupations, sometimes of delusional intensity. Multiple subtypes of delusions have also been reported, including persecutory, jealousy, religious/mystical, and grandiose. These symptoms are usually not responsive to antipsychotics in this context. Albeit less frequent, it appears that late-onset bipolar disorder with manic episodes can also be part of the prodromal phase of *C9orf72* genetic FTD, and reported cases point to good therapeutic response to lithium. Other forms of mood disturbances—including recurrent depressive episodes with or without catatonia, dysphoria with suicidal thoughts or attempts, and depression-related cognitive disturbances ("pseudodementia")—are also possible.

There are various factors that further increase the challenge of correctly identifying cases of *C9orf72* mutations in patients with late-onset psychiatric presentations:

1. Psychiatric symptoms can precede typical bvFTD features by up to 4–5 years.
2. Progression of symptoms can be slow over many years.[55,90]
3. Neuroimaging can be normal in the initial phase of the disease.[55,60,91]
4. Many subjects do not have a positive family history (either no cases or only cases of apparent primary psychiatric disorders).

Regarding point 1, Block et al.[72] proposed a model in which in some cases the psychiatric disturbance could be a prodrome of FTD during the phase of functional synaptic changes and neurotransmitter instability (i.e., psychiatric features precede FTD), whereas in others it is the result of synapse involution and cell death, thus explaining why psychiatric features start at the beginning of FTD in parallel to more typical dementia features.

It should also be mentioned that even when cognitive and neurological signs are present, they are often not restricted to the prototypical description of bvFTD or PPA as per current diagnostic criteria.[4] Indeed, patients can have early deficits in learning and recall[7] or perceptual-motor parietal dysfunction, which is incompatible with current *DSM-5* frontotemporal neurocognitive disorder criteria D requesting the relative sparing of learning and memory and perceptual-motor function. There are also cases with Parkinsonism (usually a late feature), Huntington disease-like phenotypes, and cerebellar dysfunction.[4,15,55,92] These clinical features parallel the atypical aspects of atrophy patterns that involve more parietal, cerebellar, and subcortical areas than do sporadic bvFTD. Integrating these findings together, it is unsurprising that the sensitivity of clinical bvFTD criteria is low in this population.[55,62]

Of note, increased rates of psychotic symptoms in FTD are not restricted to *C9orf72* mutations. There is a reported association with the rare frontotemporal lobar degeneration (FTLD) FUS pathology.[47] *GRN* mutations are also to an extent associated with increased psychiatric symptoms, but a recent study by Snowden et al.[61] confirmed that the rate

of psychotic symptoms, particularly somatic delusions, is higher in *C9orf72* than in *GRN* mutations.

The other clear finding from this review is that *C9orf72* mutations are very rare in patients with typical *DSM-5* schizophrenia or schizoaffective disorder (<0.1%) and bipolar disorder (approximately 0.1%). It is therefore not advisable to test patients at random. The prevalence of *C9orf72* mutation in cases of late-onset psychotic disorder or mania remains unknown, but on the basis of the epidemiology of late-onset psychotic disorders (incidence approximately 12.6 out of 100,000),[93] *C9orf72* mutations would explain only a minority of cases. However, restricting testing to patients meeting diagnostic criteria for bvFTD will clearly miss cases over periods of many years until the dementia becomes more evident. Although there are currently no curative treatments, establishing a diagnosis of neurodegenerative disease is important for families to plan personal and financial affairs prior to severe cognitive decline. It is also important to avoid potentially deleterious interventions such as high-dose antipsychotics in psychosis due to *C9orf72* mutations. It will be even more crucial to identify these patients when potential therapeutic interventions come along, while not causing prohibitive costs by testing patients at large.

The first step toward improved recognition of cases is for clinicians to be aware of this mutation and the variety of clinical presentations, including isolated psychiatric syndromes.[73] In all patients with late-onset mania, psychosis, and mood disorder with catatonia or cognitive deficits, a detailed family history should be obtained, including screening for early-onset dementia, FTD, ALS, Parkinsonism, and unexplained neuropsychiatric syndromes. Patients should have at minimum a screening cognitive assessment (e.g., Montreal Cognitive Assessment) and elemental neurological examination. Clinical symptoms of dementia, including symptoms of bvFTD and PPA, should be elicited from patients and relatives. Neuroimaging should include at minimum a cerebral CT scan, but ideally a brain MRI should be obtained to assess for early signs or cortical and subcortical atrophy. If there is a suspicion of bvFTD or other early-onset dementia, a consultation in behavioral neurology or neuropsychiatry should be obtained.

In patients with late-onset psychiatric presentations but without further clinical evidence of FTD, the question of who should be tested for *C9orf72* mutation remains open. In current practice, clinicians often wait until the appearance of clinical evidence of dementia, but the literature clearly shows that FTD features can be delayed by 4–5 years. There are currently no agreed-upon guidelines on who should be tested for the mutation in patients with late-onset psychiatric disturbances. Among patients with clinical diagnoses of frontotemporal lobar spectrum disorders, Wood et al.[94] have identified patients with high risk of genetic mutations as having either ≥1 first-degree relative (FDR) with FTLD/ALS or one second-degree relative with FTLD/ALS and one FDR with other types of dementia or Parkinson's disease or ≥2 FDRs with early-onset (≤65 years old) dementia or Parkinson's. However, restricting testing to only high-risk settings will miss cases, as many patients with *C9orf72* mutations have family history only of apparent primary psychiatric disorders.

Practices will vary according to local availability of genetic consultation and tests, but we propose the following division in terms of *C9orf72* testing for patients presenting with late-onset (after 40 years of age) psychosis, bipolar disorder, or MDD with catatonia or cognitive deficits:

Testing should be obtained if:

1. There is a history of first-degree relative with confirmed *C9orf72* mutation or with FTD spectrum disease or ALS;
2. They meet criteria for the high-risk category of Wood et al.[94];

Testing should be considered and discussed with the patient if:

3. There is a family history of late-onset bipolar or psychotic disorder or other unspecified progressive neuropsychiatric disturbance;
4. There is progressive deterioration with cognitive decline or emerging features of bvFTD, Parkinsonism, or both.

Based on the current literature, *C9orf72* testing should not be obtained in patients with *DSM-5* diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with onset prior to the age of 40 unless there is a proven genetic mutation in a first-degree relative.

We recommend a genetic consultation and counseling prior to proceeding with genetic testing. Testing by polymerase chain reaction (PCR) and Southern blot is the gold standard, as the standard repeat-primed PCR cannot distinguish repeats larger than 30–50, and blinded tests in different laboratories have showed inaccuracies.[95]

CONCLUSIONS

Clinicians need to be aware that late-onset psychosis and bipolar disorder can be the initial prodromal phase of FTD due to *C9orf72* mutations. The presentations are heterogeneous and can be difficult to identify, given their homology to primary psychiatric disorders, frequently normal imaging, and delayed appearance of more typical FTD features. Physicians need to have a high index of suspicion and elicit detailed family history of neurodegenerative diseases in those patients. This review also highlights the numerous gaps in our current knowledge (e.g., specific pathogenic mechanism, link between the mutation and psychiatric symptoms, geographic discrepancies in prevalence of psychosis, management), and much research remains to be done. Despite these limitations, we encourage psychiatrists, neurologists, geriatricians, and primary care physicians to familiarize themselves with this topic, as they have a key role in the identification of cases in inpatient and outpatient settings.

AUTHOR AND ARTICLE INFORMATION

From the Departments of Psychiatry, Neurology & Neurosurgery, Montreal Neurological Institute and McGill University Health Centre, McGill University, Montreal, Quebec, Canada (S.D.); the Department of Psychiatry and Behavioral Sciences, Stanford University Hospital, Palo Alto, Calif. (S.B.); Massachusetts General Hospital, Harvard University, Boston (B.C.D.); and the Department of Behavioural and Clinical Neurosciences, Institute of Cambridge, University of Cambridge (V.V.).

Send correspondence to Dr. Ducharme; e-mail: simon.ducharme@mcgill.ca

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