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Links Between the *C9orf72* Repeat Expansion and Psychiatric Symptoms

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Abstract

Purpose of Review To present recent findings on the links between the *C9orf72* expansion and psychiatric impairment.

Recent Findings Repeat hexanucleotide expansions in the *C9orf72* gene are a cause of familial frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and the mixed phenotype, FTD-ALS. Symptomatic expansion carriers display higher rates of psychotic and other psychiatric symptoms than non-carriers. Neuroanatomical associations of these symptoms have been found in cortical and subcortical areas. Family members of symptomatic carriers have higher rates of primary neuropsychiatric disorders than control populations, and the *C9orf72* expansion may contribute to this association. However, the expansion does not appear to directly cause primary psychiatric disorders.

Summary While there is strong evidence associating the *C9orf72* expansion with psychotic symptoms in carriers and psychiatric disorders in their kindreds, the link between these two phenomena, if any, remains unclear.

Keywords *C9orf72* · Psychiatric · Frontotemporal dementia · Amyotrophic lateral sclerosis

Introduction

In 2011, a hexanucleotide repeat expansion in the *C9orf72* gene was identified as a pathogenic cause of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and the mixed phenotype, FTD-ALS [1, 2]. The expansion is the most common cause of genetic ALS and FTD, responsible for 23–38% of familial ALS, 20–25% of familial FTD, and up to 50% of familial FTD-ALS cases [3•, 4, 5]. In addition, the expansion accounts for approximately 3–6% of sporadic ALS and 2–6% of sporadic FTD [3•, 4, 6]. These numbers vary between ethnic groups, with higher rates among Caucasians and lower rates in Asian populations [3•, 6].

The *C9orf72* mutation is autosomal dominant, and carriers within genetic families may display ALS, FTD, FTD-ALS, or other less common disorders [3•]. Multiple phenotypes are typically present within single mutation-carrying families [3•]. The mutation shows age-dependent, high penetrance with a median age of onset in the sixth decade. Cumulative penetrance ranges from 90.9 to 95.5% by age 83 [7]. However, there are reported cases of mutation carriers remaining asymptomatic into their ninth decade, indicating that penetrance may be incomplete [7]. Average incidence of the repeat expansion across healthy adult populations is estimated at 0.06% [7], and is as high as 0.15% in one British population study [8].

The typical number of expansion repeats in the *C9orf72* gene in healthy adults ranges from around 1 to 20, although higher numbers have been reported [8, 9]. Patients with the pathogenic mutation will often have repeat numbers in the hundreds or thousands [9, 10]. The implications of an intermediate number of repeats (generally considered 20–30) are undetermined [11]. There is dispute over the specific number of repeats that constitutes pathogenicity; however, estimates range between 30 and 60 [9, 10]. Part of the uncertainty stems from the possibility of somatic expansion, i.e. that repeat lengths in DNA collected from brain tissue can vary from repeat lengths

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in DNA collected from blood and other organs—and that this variation can occur even in DNA collected from tissue in different brain regions [12]. These differences in repeat length have been shown both across groups and within individuals from whom multiple samples were collected [12]. Repeat number in a patient population has not been shown to associate with age of onset, disease duration, or clinical phenotype (ALS or FTD) [9, 11], perhaps because of this variation in repeat number within an individual [12]. Additionally, there is debate about whether or not anticipation, defined as earlier age at onset in progeny, occurs through generations [10, 13].

Mechanisms of toxicity of the *C9orf72* expansion are not established, but both loss of function and gain of function mechanisms have been proposed [14••, 15]. The pathology due to *C9orf72* expansions is characterized by TAR DNA-binding protein 43 (TDP-43) inclusions (typically type B) in regions equivalent to those found in sporadic FTLD-TDP and ALS [1, 10]. In addition, inclusions containing dipeptide repeat (DPR) proteins resulting from the translation of the expanded gene have been found in both cortical and subcortical regions, as well as in the cerebellum [16, 17]. While TDP-43 pathology is not specific to the *C9orf72* mutation, the DPR protein pathology does appear to be a specific feature and may confer unique mechanisms of toxicity [14••, 18]. Atrophy in patients with ALS and FTD due to *C9orf72* tends to be symmetrical and to include more parietal, subcortical (e.g., thalamus), and cerebellar regions than are seen in non-carriers with these diseases [10, 19, 20].

Psychotic Symptoms in *C9orf72* Expansion Carriers

Clinical characterizations of *C9orf72* mutation carriers with FTD and FTD-ALS have shown that carriers have higher rates of psychotic symptoms (delusions and hallucinations) than non-carriers [14•]. The most common clinical phenotype of FTD due to the *C9orf72* mutation is behavioral variant FTD (bvFTD) [10]. Reports of psychotic symptoms across FTD groups vary, but they are present in approximately 3.5% of all cases of bvFTD, and in up to 10% of all FTLD cases, including FTD-ALS [21, 22]. However, the presence of such symptoms in *C9orf72* expansion carriers with FTD (including bvFTD and FTD-ALS) ranges from 21 to 56% [14•]. The *C9orf72*-related psychotic symptoms are often somatic in nature, such as one patient's complaint of plastic emanating from his head [23–25]. It has been hypothesized that the preponderance of somatic delusions may be due to an altered body schema (e.g., impaired tactile encoding, proprioception, and representation of body parts), associated with the posterior, subcortical, and cerebellar atrophy seen in *C9orf72* carriers [26]. Case reports demonstrate that psychotic symptoms may occur prodromally years prior to formal diagnosis of FTD, which can lead to misdiagnosis of a psychiatric disorder such as schizophrenia [27–30]. Interestingly, other genetic variants of FTD may have their own unique psychiatric symptoms, including visual hallucinations in patients with mutations in the *GRN* gene [21], or depressive symptoms prior to an FTD diagnosis in some carriers of *MAPT* mutations [31].

A few studies have investigated possible genetic modifiers of the psychotic phenotype in *C9orf72*-linked FTD. One study identified a 10 base pair deletion adjacent to the *C9orf72* expansion; carriers without this deletion were significantly more likely to have psychotic symptoms [32]. Another study found that an intermediate number of repeats (20–30) was associated with psychotic symptoms in FTD and other dementias [11]. However, these hypotheses are based on small samples and necessitate more thorough exploration.

Psychiatric symptoms often precede motor symptoms in patients with ALS [33]. Patients hospitalized for schizophrenia, bipolar disorder, depression, or anxiety are significantly more likely to develop ALS within the following year than patients hospitalized for other reasons [34•], and rates of depression, neurotic disorders, and drug abuse/dependence are higher in patients with ALS, both before and after diagnoses than in healthy controls [35•]. Unlike with FTD, there is no established association between these psychiatric symptoms and the *C9orf72* expansion in ALS (the referenced studies did not have access to genetic data on the participants), and the possibility of a unique psychiatric profile in carriers with ALS has not been explored.

Neuroanatomical Associations with Psychiatric Symptoms in *C9orf72* Carriers with FTD/FTD-ALS

Recent studies have investigated the neuroanatomical associations of psychiatric symptoms in *C9orf72* carriers with bvFTD and FTD-ALS [36••, 37••]. In a sample of mutation carriers, psychotic symptoms (delusions and hallucinations) were associated with a pattern of cortical and subcortical gray matter volume loss in regions within the medial-frontal, temporal, and occipital cortices, anterior cingulate cortex, insula, basil ganglia, thalamic nuclei, and right cerebellum [36••]. These associations were more widespread when compared to the combined group of mutation and non-mutation patients, for whom psychotic symptoms correlated with reduced volume in the medial prefrontal cortex, occipital cortices, right thalamus, and left cerebellum. Note that in this study, analyses were not run for the non-carriers alone.

Another study used voxel-based morphometry (VBM) to find neuroanatomical associations of individual psychiatric symptoms in *C9orf72* carriers [37••]. Visual hallucinations were associated with posterior atrophy, including the left parietal lobe and occipital pole, whereas delusions and tactile and auditory hallucinations were associated with frontal atrophy.

Depression and anxiety were associated with frontal, parietal, and cerebellar atrophy. Unique associations between psychiatric symptoms and volume loss in differing regions were also found in carriers of mutations is two other FTD-related genes, *MAPT* and *GRN*. These include associations between psychotic symptoms and atrophy in the left thalamus, left middle frontal gyrus, and cerebellum in *GRN* mutation carriers, with atrophy of the temporal lobe and angular gyri in *MAPT* mutation carriers, and with atrophy of the anterior insula in both groups. However, the generalizability of these findings is limited by the small sample size for each symptom.

A clinicopathological study of FTD patients with *C9orf72* mutations identified greater volume loss in the left parietal precuneus in four patients with delusions than in 13 patients who did not have delusions [30]. In combination with the findings above, this indicates that delusions may be associated with both frontal and posterior atrophy. More generally, psychotic symptoms in *C9orf72* carriers seem to be associated with widespread atrophy in frontal and posterior regions, as well as in subcortical regions (e.g., the thalamus) and even the cerebellum. However, given the small sample sizes of the studies and the large range of areas identified, it is difficult to interpret the neuroanatomical underpinnings of these symptoms more definitively, and larger groups will be needed for a thorough characterization.

Several of the regions identified in the above analyses, including the thalamus and cerebellum, show reduced gray matter volume in *C9orf72* carriers with bvFTD compared to other mutation carriers and sporadic non-carriers of comparable age, gender, phenotype, and disease duration [10, 19, 20]. In addition, gray matter volume differences between clinically normal *C9orf72* expansion carriers from FTD families and familial normal controls have been identified in carriers as far as 25 years from their expected age of onset [38]. Specifically, carriers had reduced volume in the thalamus, insula, and posterior cortical areas 25 years prior to expected age of onset, reduced volume in frontal and temporal lobes 20 years prior to expected onset, and reduced cerebellar volume 10 years prior to expected onset. Note, however, that the sample in this study only included five asymptomatic individuals more than 25 years from their expected age of onset, so it remains to be established if the findings are generalizable. It is not known whether the structural changes in *C9orf72* mutation carriers who have not yet progressed to bvFTD or FTD-ALS may relate to the psychotic symptoms that can present early in (or prior to) the manifestation of their disease.

C9orf72 Expansion in Primary Psychiatric Disorders

Considering the high prevalence of psychotic symptoms in symptomatic *C9orf72* carriers, a few studies have explored whether the repeat expansion is present in populations with psychotic and other primary psychiatric disorders. Across several studies including cohorts from the USA, Ireland, Finland, and Japan, a total of 2687 patients with schizophrenia, schizoaffective disorder, or other psychosis have been screened for the mutation [39, 42, 43•, 44•]. Of these, five individuals with schizophrenia or schizoaffective disorder (0.19% of the total patients) have been identified with a pathogenic number of repeats (> 30) [40, 44•]. Four cohorts of patients with bipolar disorder in the US and Europe, encompassing 862 patients, have also been screened for the mutation [41, 45, 46, 47]. Of these, two have been identified as having a pathogenic number of repeats (0.23% of the patients). More recently, samples of 573 patients with obsessive-compulsive disorder and 109 individuals who died by suicide have been screened for the expansion, with no members of either group carrying the pathogenic mutation [48•, 49•].

While it is possible that the *C9orf72* expansion is a rare cause of schizophrenia, schizoaffective disorder, and bipolar disorder, it does not appear to be a significant cause of these, nor of other psychiatric diseases. The prevalence of the repeat expansion in these psychiatric cohorts was only slightly greater than the prevalence found in healthy controls (up to 0.15%) [8]. Therefore, it is not clear that the expansions detected in the above cohorts were causative of the patients' psychiatric impairment.

Psychiatric Disease in ALS and FTD Kindreds

Recent population studies of first- and second-degree relatives ("kindreds") of patients with both sporadic and familial ALS show elevated rates of primary psychiatric disorders. Specifically, these kindreds have significantly higher risks of psychotic disorder and death by suicide [50], as well as of schizophrenia, autism spectrum disorder (ASD), and alcoholism [51••], compared to kindreds of healthy controls, see Table 1. When kindreds of *C9orf72* expansion carriers were directly compared with kindreds of patients with sporadic ALS, they showed significantly higher risks of a psychotic disorder and death by suicide. Risks of the other diagnoses were not compared. In a small FTD cohort, *C9orf72* carriers were more likely to have a family history of psychiatric disorders (schizophrenia, depression, and suicide) than non-carriers [52].

A more recent study looking at kindreds of patients with both ALS and FTD showed that risk of psychiatric illnesses (schizophrenia, late-onset psychosis unrelated to schizophrenia, suicide, and ASD) was significantly greater in kindreds of *C9orf72* expansion carriers than in kindreds of non-carriers, with no group difference in risk of mood disorders [53••]. Rates of disorders in kindreds did not differ based on the diagnosis (FTD or ALS) of the proband, with the exception

Table 1 Kindred studies in ALS and FTD families

Study	Groups examined	Psychiatric diagnoses accounted for in kindreds	Significant findings ($p < 0.05$; CI = 95%)
Byrne et al. 2013	*Probands* *N* = 172 probands with ALS • 17 with C9 mutation *N* = 192 control probands *Kindreds* *N* = 4050 case kindreds • 401 C9 carrier kindreds *N* = 5634 control kindreds	Depression, schizophrenia/psychotic illness, suicide	*ALS kindreds vs. control kindreds*: • ALS kindreds had an increased HR of developing schizophrenia/psychotic illness (HR = 4.7; CI 2.5–6.7) and of suicide (HR = 5.6; CI 2.4–12.9) *ALS C9 carrier kindreds vs. non-carrier kindreds*: • Carrier kindreds had an increased risk of schizophrenia/psychotic illness (HR = 9.9; CI 4.8–20.5) and death by suicide (HR = 16; CI 5.9–46.4)
Devenney et al. 2014	*Probands* *N* = 84 probands with FTD *N* = 23 probands with FTD-ALS • 14 with C9 mutation across both groups *Kindreds* *N* not given	Not specified	*FTD/FTD-ALS C9 carrier kindreds vs. non-carrier kindreds*: • Psychiatric illness (schizophrenia, depression, suicide) was more common in carriers than in non-carriers (4 vs. 1, respectively)
O'Brien et al. 2017	*Probands* *N* = 127 probands with ALS • 21 with C9 mutation *N* = 132 control probands *Kindreds* *N* = 2116 case kindreds *N* = 2139 control kindreds	Depression, schizophrenia/psychotic illness, suicide, ASD, OCD, alcoholism	*ALS kindreds vs. control kindreds*: • ALS kindreds had increased RR of schizophrenia/psychotic (RR = 3.40; CI 4.8–20.5), suicide (RR = 3.30; CI 1.07–10.05), ASD (RR = 10.10; CI 1.30–78.80), OCD (RR = 5.60; CI 1.23–25.05), and alcoholism (RR = 1.48; CI 1.01–2.17), and probands had higher rate of having 3+ family members with psychiatric illness *ALS C9 carrier kindreds vs. non-carrier kindreds*: • No difference in rate of having 3+ family members with psychiatric illness. No other direct comparisons made
Longinetti et al. 2017	*Probands* *N* = 3648 probands with ALS *N* = 36,480 control probands *Kindreds* *N* = 19,760 case kindreds *N* = 198,794 control kindreds	Schizophrenia, bipolar disorder, depression, neurotic disorders, stress-related disorders, alcohol abuse/dependence, drug abuse/dependence	*ALS kindreds vs. control kindreds*: • Children of patients with ALS (but not parents or siblings) had higher risk of psychiatric disorders both before and after diagnosis of the proband (HR = 1.11; CI 1.00–1.25)
Devenney et al. 2018	*Probands* *N* = 46 probands with FTD *N* = 43 probands with ALS • 29 with C9 mutation across both groups *Kindreds* *N* = 1414 carrier kindreds	Schizophrenia, psychosis, mood disorder, bipolar disorder, suicide, ASD	*C9 carrier kindreds vs. non-carrier kindreds*: • Carrier kindreds had a greater HR of schizophrenia (HR = 4.9; CI 1.7–13.9), late-onset psychosis (HR = 17.9; CI 2.2–143.2), suicide (HR = 2.7; CI 1.2–6.2), and ASD (HR = 2.7; CI 1.1–6.9)

HR hazard ratio, *RR* relative risk

of autism spectrum disorder, which was more common in kindreds of *C9orf72* carriers with FTD. Within the *C9orf72* carrier cohort, probands with early psychotic symptoms were more likely to have kindreds with psychiatric diagnoses than those without psychotic symptoms ("early" is not defined in the paper). Interestingly, several expansion carriers with no family history of neurodegenerative disease did have family histories of psychiatric disease.

Taken together, these findings indicate a possible connection between the *C9orf72* repeat expansion and familial psychiatric disorders. Yet the nature of this association is unclear. First, the expansion appears to account for some but not all of the association between ALS and familial psychiatric disorders [50, 51••]. This agrees with a recent finding that ALS and schizophrenia share 14% of their polygenic risk, an overlap only partly explained by a locus corresponding to the *C9orf72* gene [54•]. Second, for the above studies, family history was determined by report, and no genetic information was obtained on kindreds. For this reason, it is unclear what proportion of the kindreds were themselves carriers of the *C9orf72* expansion or at risk of developing a neurodegenerative disease. Given the evidence of psychiatric prodromes in both FTD and ALS, as well as the neuroanatomical changes that occur decades prior to diagnosis in *C9orf72* carriers, some of the reported psychiatric diseases may in fact have reflected early symptoms of a neurodegenerative process. This is especially worth considering, as familial psychiatric illness was highest for probands who themselves experienced early psychotic symptoms. Furthermore, there is a preponderance of evidence for the early misdiagnosis of FTD as psychiatric disease [55].

Importantly, psychiatric disorders are common in the general population, with 46% of Americans meeting criteria for a psychiatric disorder in their lifetimes [56]. They are also highly heritable, with estimates of the variance explained by genetic factors ranging from 23 to 76% for schizophrenia, 25 to 58% for bipolar disorder, 49 to 56% for ASD, and 21 to 32% for major depression [57, 58]. Furthermore, several of these disorders—including many referenced in the kindred studies above—share genetic risk (e.g., bipolar disorder with schizophrenia, both bipolar disorder and schizophrenia with major depression, and ASD with schizophrenia), indicating the presence of common variants [57, 58]. Therefore, the possibility of coincident psychiatric illnesses running in the *C9orf72* expansion families cannot be ruled out. Moderate proband sample sizes in the studies above make such a coincidence more likely.

Furthermore, *C9orf72* probands are more likely to have *other* family members with neurodegenerative disease than non-carriers [53••], meaning kindreds of these probands may be exposed to more social and environmental stressors than kindreds of probands with sporadic disease. This could in turn lead to complex developments in the lifetime psychiatric symptoms of those kindreds. For example, being the caregiver to someone with dementia is associated with increased stress and depression [59, 60], and young children of patients may have complex psychological effects from witnessing their parents' decline [61, 62]. Kindreds of genetic probands may also be at risk of carrying the mutation themselves, the knowledge of which could contribute to anxiety and emotional distress, as has been described in Huntington's disease [63].

Clinical Implications

The findings described above have important implications for clinicians treating patients with FTD and ALS. Late-life psychosis should be investigated as a possible prodrome of a neurodegenerative illness. Genetic testing can be offered to rule in or out *C9orf72*, particularly in patients with a family history of a dementia, ALS, or late-onset psychiatric disease. Because of the possibility of mutations in such genes as *GRN,* genetic testing should include both testing for the *C9orf72* expansion and a next-generation sequencing panel of other FTD genes. These tests can be run either concurrently or sequentially if the *C9orf72* test is negative. Genetic counseling should be performed prior to testing, in order to explain implications for the patient and for other family members. In particular, families should be informed about the inter- and intra-familial phenotypic variability associated with these genes, so that it is not possible to predict age of onset, types of symptoms, or disease course.

There are no established recommendations for medical management of psychotic symptoms in patients with *C9orf72* mutations. Case reports have generally failed to show positive effects of antipsychotic medication in carries with FTD, and have shown a high incidence of adverse effects of the medication [25, 64, 65]. There are few studies on the efficacy of antipsychotic medication in sporadic FTD, and in most of those studies, the antipsychotic medication was targeted toward agitation rather than psychosis specifically [66].

Conclusions

Since the discovery of the *C9orf72* expansion and its causative role in ALS and FTD, an association with psychotic symptoms in expansion carriers has been shown within the FTD population. Novel research has further characterized the nature of this association, with preliminary investigations highlighting the possibility of genetic modifiers of psychotic symptoms, and imaging analyses showing associations between psychiatric symptoms and regional atrophy. Future research will need to investigate these effects among larger patient samples. Similarly, it remains to be investigated if *C9orf72* mutation carriers with ALS also present with higher

rates of psychotic symptoms or with a psychiatric prodrome, as is seen in FTD and FTD-ALS.

Research has failed to identify the *C9orf72* expansion as a significant cause of primary psychiatric illness. Despite this, novel, population-based studies show that *C9orf72* mutation carriers with ALS and FTD have a higher prevalence of familial psychiatric disease than phenotypically-matched non-carriers. Future investigations of genetic modifiers of this association in family members and of potential shared genetic variance between ALS, FTD, and psychiatric disorders in *C9orf72* mutation carriers would help to clarify any *C9orf72* mediated cause of psychiatric symptoms.

The precise mechanisms underlying psychiatric symptoms in *C9orf72* mutation carriers, as well as psychiatric disease in their relatives, remain unclear, as does the potential relationship between these phenomena. Refinement of our understanding of the relationship between the *C9orf72* repeat expansion and psychiatric impairment will have practical implications for clinicians and researchers alike.

Compliance with Ethical Standards

Conflict of Interest Hannah E. Silverman, Jill S. Goldman, and Edward D. Huey each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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