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# *C9orf72* Frontotemporal Dementia and/or Amyotrophic Lateral Sclerosis

Synonym: *C9orf72*-FTD/ALS

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## Summary

### Clinical characteristics

*C9orf72* frontotemporal dementia and/or amyotrophic lateral sclerosis (*C9orf72*-FTD/ALS) is characterized most often by frontotemporal dementia (FTD) and upper and lower motor neuron disease (MND); however, atypical presentations also occur. Age at onset is usually between 50 and 64 years (range: 20-91 years) irrespective of the presenting manifestations, which may be pure FTD, pure amyotrophic lateral sclerosis (ALS), or a combination of the two phenotypes. The clinical presentation is highly heterogeneous and may differ between and within families, causing an unpredictable pattern and age of onset of clinical manifestations. The presence of MND correlates with an earlier age of onset and a worse overall prognosis.

### Diagnosis/testing

The diagnosis of *C9orf72*-FTD/ALS is established in a proband with suggestive findings and a heterozygous abnormal $G_4C_2$ (GGGGCC) hexanucleotide repeat expansion in *C9orf72* identified by molecular genetic testing.

### Management

*Treatment of manifestations:* Care is often provided by a multidisciplinary team that includes a neurologist, specially trained nurses, pulmonologist, speech therapist, physical therapist, occupational therapist, respiratory therapist, nutritionist, psychologist, social worker, and genetic counselor.

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*Surveillance:* Routine follow up by multidisciplinary specialists to monitor neurologic findings, mobility and activities of daily living, psychiatric/behavioral manifestations, nutrition and safety of oral feeding, respiratory and bladder function, and needs of affected individuals and care providers for psychosocial support.

## Genetic counseling

*C9orf72*-FTD/ALS is inherited in an autosomal dominant manner. Almost all individuals diagnosed with *C9orf72*-FTD/ALS inherited a *C9orf72* $G_4C_2$ repeat expansion from a heterozygous parent. In most families the heterozygous parent is affected; however, a heterozygous parent may not have clinical manifestations of the disorder due to age-dependent reduced penetrance. Each child of an individual with *C9orf72*-FTD/ALS has a 50% chance of inheriting the *C9orf72* $G_4C_2$ repeat expansion. Once a *C9orf72* $G_4C_2$ repeat expansion has been identified in an affected family member, prenatal and preimplantation genetic testing for the presence of the *C9orf72* $G_4C_2$ repeat expansion are possible. (Note: The presence of a *C9orf72* $G_4C_2$ repeat expansion cannot predict the disease course in any given individual.)

# Diagnosis

In this *GeneReview*, *C9orf72* frontotemporal dementia and/or amyotrophic lateral sclerosis (*C9orf72*-FTD/ALS) refers to the spectrum of phenotypes caused by *C9orf72* $G_4C_2$ pathogenic repeat expansions, also sometimes referred to as the *C9orf72* FTD/ALS complex.

## Suggestive Findings

*C9orf72*-FTD/ALS **should be suspected** in probands with the following clinical and neuroimaging findings and family history [Van Mossevelde et al 2018, Cammack et al 2019, Moore et al 2020].

### Clinical Findings

**Age at onset** ranges from 20 to 91 years, with a mean of 58 ± 8-10 years [Van Mossevelde et al 2017a].

**Neurologic findings** (See also Table 1.)

- **Frontotemporal dementia (FTD),** the most common clinical presentation, is characterized by progressive behavioral impairment, decline in executive function, and/or language impairment (see Table 1). Of the three FTD clinical syndromes, behavioral variant FTD (bvFTD) is more often present than the two language variants (collectively identified as primary progressive aphasia [PPA]: semantic variant PPA [svPPA] and non-fluent variant PPA [nfvPPA]).

  Manifestations specific to *C9orf72*-FTD include prominent neuropsychiatric symptoms, such as hallucinations and delusions. Often, some parkinsonian features are present.

- **Motor neuron disease** includes both the upper and lower motor neuron involvement that characterizes amyotrophic lateral sclerosis (ALS) as well as upper and/or lower motor neuron dysfunction that may or may not fulfill criteria for the full ALS phenotype.

- **Atypical presentations** mimicking other neurodegenerative disorders

**Table 1.** *C9orf72*-FTD/ALS: Frequency of Diagnoses Based on Clinical Findings Alone

| Diagnosis | Frequency | Comments (Frequency) |
|---|---|---|
| FTD | 34.8% | • Behavioral variant FTD (31.4%)<br>• Nonfluent/agrammatic variant PPA (1.8%)<br>• Semantic variant PPA (0.9%)<br>• Other tauopathy: corticobasal degeneration, progressive supranuclear palsy, other PPA (0.7%) |

*Table 1. continued from previous page.*

| Diagnosis | Frequency | Comments (Frequency) |
|---|---|---|
| ALS | 19.3% | |
| FTD-ALS | 11.0% | |
| Atypical presentations mimicking other kinds of neurodegenerative brain diseases | 35.0% | • Alzheimer disease, Parkinson disease, Huntington disease, & dementia w/Lewy bodies are common.<br>• Also incl vascular dementia & dementia not otherwise specified<br>• Atypical parkinsonian syndromes [1] |

Based on Moore et al [2020]
ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia; PPA = primary progressive aphasia
*1.* Van Mossevelde et al [2018]

## Neuroimaging

**Brain MRI.** The pattern of atrophy in *C9orf72*-FTD is remarkably symmetric and generalized. Cortical atrophy can be seen in the frontal and temporal regions, also the insular and cingulate regions, as well as more posterior cortical areas. Also notable is involvement of subcortical structures and the cerebellum [Cash et al 2018, Van Mossevelde et al 2018].

**Brain FDG-PET.** The pattern of predominant frontotemporal hypometabolism is mostly congruent with the atrophy patterns seen on brain MRI; however, FDG-PET abnormalities can usually be detected earlier than suggestive brain MRI findings [Greaves & Rohrer 2019].

**CSF biomarkers.** Nonspecific abnormalities in Alzheimer disease CSF biomarkers, such as (slightly) increased levels of total tau or decreased levels of amyloid beta 1-42, may or may not be present [Niemantsverdriet et al 2018].

## Family History

Family history may be positive and consistent with autosomal dominant inheritance (e.g., males and females in multiple generations with ALS, FTD, and/or other manifestations within the *C9orf72*-FTD/ALS spectrum) or the family history may be negative; absence of a known family history does not preclude the diagnosis. *C9orf72* $G_4C_2$ repeat expansions are to date the most frequent cause of ALS and FTD in individuals representing simplex cases (i.e., a single occurrence within a family) [Van Mossevelde et al 2018].

Note: Simplex cases are sometimes referred to as "sporadic cases"; however, because the term "sporadic" can imply a non-recurring (non-genetic) cause, the term "simplex" is preferred.

# Establishing the Diagnosis

The diagnosis of *C9orf72*-FTD/ALS **is established** in a proband with suggestive findings and a heterozygous abnormal $G_4C_2$ (GGGGCC) hexanucleotide repeat expansion in *C9orf72* identified by molecular genetic testing [DeJesus-Hernandez et al 2011, Renton et al 2011, Gijselinck et al 2012] (see Table 2).

Note: Pathogenic $G_4C_2$ repeat expansions in *C9orf72* **cannot be detected** by sequence-based multigene panels, exome sequencing, or genome sequencing.

**Repeat sizes**

- **Normal.** Range from 2 to 24 $G_4C_2$ repeats
- **Uncertain significance.** Range from 25 to 60 $G_4C_2$ repeats

- Repeats in this range are rare in the general population and typically do not segregate in families with *C9orf72*-FTD/ALS.
- The shortest $G_4C_2$ repeat identified in white blood cells and reported to cosegregate with the disorder in a family with *C9orf72*-FTD/ALS was 47 $G_4C_2$ repeats [Gijselinck et al 2016]. However, in different brain regions of the individual who was heterozygous for the short expansion, a pool of short and long expansion sizes (>1100 repeat units) was apparent, pointing to somatic mosaicism [Gijselinck et al 2016].

- **Pathogenic.** Range from 61 to >4000 of $G_4C_2$ repeats

  Pathogenic expansions >60 to hundreds or thousands of $G_4C_2$ repeats show age-dependent reduced penetrance [Murphy et al 2017].

**Molecular genetic testing** relies on targeted analysis to characterize the number of *C9orf72* $G_4C_2$ repeats (see Table 8).

**Table 2.** Molecular Genetic Testing Used in *C9orf72*-FTD/ALS

| Gene [1] | Method [2, 3] | Proportion of Probands with a Pathogenic Variant Detectable by Method |
|---|---|---|
| *C9orf72* | Targeted analysis for $G_4C_2$ hexanucleotide expansions | 100% |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Table 8 for specific methods to characterize the number of GGGGCC ($G_4C_2$) repeats in *C9orf72*.
*3.* Note: Sequence-based multigene panels, exome sequencing, and genome sequencing cannot detect pathogenic repeat expansions in this gene.

# Clinical Characteristics

## Clinical Description

*C9orf72* frontotemporal dementia and/or amyotrophic lateral sclerosis (*C9orf72*-FTD/ALS) is characterized most often by frontotemporal dementia (FTD) and upper and lower motor neuron disease (MND); however, atypical presentations also occur. Mean age at onset is usually 50-64 years (range: 20-91 years) irrespective of the presenting manifestations, which may be pure FTD, pure ALS, or a combination of the two phenotypes. The clinical presentation is highly heterogeneous and may differ between and within families, causing an unpredictable pattern and age of onset of clinical manifestations (see Table 3). The presence of MND correlates with an earlier age of onset and a worse overall prognosis [Van Mossevelde et al 2018, Moore et al 2020].

Like the age of onset, life expectancy is highly variable and mainly associated with the clinical manifestations.

**Table 3.** *C9orf72*-FTD/ALS: Frequency of Disease Features

| Feature | Frequency | | | Comment |
|---|---|---|---|---|
| | Nearly all | Common [1] | Infrequent | |
| **Cognitive deterioration** | | | | |
| Executive dysfunction | ● | | | Issues w/planning, problem solving, organizing |
| Memory impairment | | ● | | Amnesia, mostly recent memory |
| Language impairment | | ● | | Deficits in speech production or comprehension |
| Apraxia | | ● | | Impaired execution of learned motor tasks |
| Dyscalculia | | ● | | Diminished mathematical reasoning |
| **Behavioral & psychological manifestations of dementia** | | | | |

*Table 3. continued from previous page.*

| Feature | | Frequency | | | Comment |
|---|---|---|---|---|---|
| | | Nearly all | Common [1] | Infrequent | |
| Disinhibition | | | ● | | Impulsivity, socially unacceptable behavior, risk taking |
| Apathy | | | ● | | Indifference, lack of interest |
| Delusions/hallucinations | | | ● | | Often bizarre delusions, mostly visual hallucinations |
| Psychosis | | | ● | | Psychosis, often as initial symptom |
| Anxiety | | | ● | | Generalized stress & apprehension |
| Repetitive, compulsive behavior | | | ● | | Often complex, ritualistic behaviors mimicking OCD |
| Preference for sweet food | | | | ● | ↑ craving for sweet foods |
| **Motor symptoms** | | | | | |
| Upper MND | | | ● | | Weakness, spasticity, altered muscle tone |
| Lower MND | | | ● | | Weakness, fasciculations, atrophy |
| Bulbar involvement | Dysarthria | | | ● | Motor language deficit |
| | Dysphagia | | | ● | Problems swallowing food &/or liquids |
| Parkinsonism | | | ● | | Extrapyramidal findings such as resting tremor, rigidity, akinesia |

MND = motor neuron disease; OCD = obsessive compulsive disorder
*1.* Features are ranked as common if present in >33%, if frequency was mentioned.

Initial manifestations may be pure FTD or ALS; additional manifestations in the *C9orf72*-FTD/ALS spectrum may appear during the disease course [Van Mossevelde et al 2018, Moore et al 2020].

## FTD

The three main FTD clinical syndromes are behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent/agrammatic variant PPA (nfvPPA). Most individuals with *C9orf72*-FTD and *C9orf72*-FTD/ALS present with bvFTD.

Cognitive deficits associated with FTD are mostly early loss of executive functions, memory impairment, and language problems (mostly dynamic aphasia). Other findings, such as parietal lobe involvement (dyscalculia, apraxia), are common as the disease progresses.

*C9orf72*-bvFTD includes most of the typical bvFTD behavioral changes: early disinhibition, early apathy or inertia, early loss of empathy, as well as repetitive and ritualistic behaviors. Although sweet food preference occurs, it is less common. Other prominent neuropsychiatric symptoms include early delusions and hallucinations, psychosis, and anxiety.

*C9orf72*-PPA presents with early and prominent language deficits – speech apraxia and frequent grammatical errors in the more common nfvPPA or decreased understanding of language in svPPA.

## ALS

The entire clinical spectrum of ALS (which includes abnormal muscle tone and tendon reflexes, fasciculations, muscle cramps, and gait disturbances) may be present in *C9orf72*-ALS and *C9orf72*-FTD/ALS. Spinal onset (involving limb muscles) is more frequent than bulbar onset (including involvement of swallowing and speech) in *C9orf72*-ALS (54% vs 39%). Some early cognitive impairment may be present even in individuals who had

been diagnosed with pure ALS [Cammack et al 2019]. See Amyotrophic Lateral Sclerosis Overview for a definition of this phenotype.

### Atypical Presentations

Atypical presentations of the *C9orf72*-FTD/ALS spectrum mimicking other neurodegenerative brain diseases – including Alzheimer disease, Parkinson disease, Huntington disease (see linked *GeneReview* chapters for definitions of these phenotypes), and dementia with Lewy bodies – are common. In addition to MND, motor manifestations may also include extrapyramidal signs, most commonly as a symmetric akinetic-rigid syndrome. Clinical diagnoses of atypical parkinsonian syndromes are also relatively common.

A *C9orf72* pathogenic $G_4C_2$ repeat expansion is seen in fewer than 1% of individuals with clinically diagnosed Alzheimer disease (AD). In most of these individuals, the underlying pathology is frontotemporal lobar degeneration (FTLD) [Murray et al 2011, Dobson-Stone et al 2012, Majounie et al 2012a, Cacace et al 2013, Harms et al 2013, Kohli et al 2013]. Similar observations were made in individuals with clinical Parkinson disease (PD) [Lesage et al 2013, Theuns et al 2014, Wilke et al 2016].

The association of *C9orf72* $G_4C_2$ pathogenic repeat expansions with AD, PD, and atypical parkinsonian syndromes may be due to relatively common AD or PD co-pathology occurring in an individual with primary *C9orf72*-related disease. Moreover, most of the studies reporting on this association defined cohorts of affected individuals solely on clinical diagnoses, leaving the possibility of misclassification of an individual with *C9orf72*-FTD [Lesage et al 2013, Theuns et al 2014, Wilke et al 2016].

A *C9orf72* $G_4C_2$ repeat expansion was observed in 6.5% of individuals with a diagnosis of depressive pseudodementia [Bieniek et al 2014] and in 2% of Huntington disease phenocopies lacking an *HTT* CAG trinucleotide repeat expansion [Beck et al 2013, Hensman Moss et al 2014].

Rarely, *C9orf72*-related corticobasal syndrome, progressive supranuclear palsy, and olivopontocerebellar degeneration have also been reported [Snowden et al 2012, Lesage et al 2013, Lindquist et al 2013, Schottlaender et al 2015, Wilke et al 2016, Bourinaris & Houlden 2018, Cali et al 2019].

### Life Expectancy

Life expectancy for individuals with *C9orf72*-FTD/ALS is highly variable and mainly associated with an individual's clinical features. Overall disease duration averages 6.4 years (range 0-36), which is significantly lower than in individuals with *GRN* frontotemporal dementia and *MAPT* frontotemporal dementia [Moore et al 2020].

- For *C9orf72*-ALS, $G_4C_2$ repeat expansions are associated with an average disease duration of 2.9 ± 2.8 years [Cammack et al 2019, Moore et al 2020].
- For *C9orf72*-FTD, disease duration averages between 7.5 and 14 years, depending on the cohort. As expected, survival in FTD is markedly compromised (on average 1.8 years) when ALS manifestations become apparent [Van Mossevelde et al 2018, Moore et al 2020].

## Genotype-Phenotype Correlations

**Heterozygous expanded $G_4C_2$ repeats.** Clinical findings cannot predict the presence or size of a *C9orf72* $G_4C_2$ repeat expansion, nor can the presence of a $G_4C_2$ repeat expansion predict the disease course in any given individual.

**Biallelic expanded $G_4C_2$ repeats.** To date, one individual homozygous for an expanded *C9orf72* $G_4C_2$ repeat has been reported. This individual (whose parents were consanguineous) was homozygous for >800 $G_4C_2$ repeats and presented with early-onset bvFTD at age 43 years followed by rapid deterioration that was nonetheless within the range of the usual disease spectrum [Fratta et al 2013].

Another individual, compound heterozygous for two expanded alleles (one with ±50 $G_4C_2$ repeats and one with >2000 $G_4C_2$ repeats), had onset age of 58 years of bvFTD associated with parkinsonism [Cooper-Knock et al 2013].

## Penetrance

Heterozygosity for a pathogenic *C9orf72* $G_4C_2$ repeat expansion is associated with age-dependent reduced penetrance, with the youngest individuals developing disease in their twenties and a small number of heterozygotes remaining asymptomatic in their nineties. Age-dependent penetrance is estimated as follows [Benussi et al 2015, Murphy et al 2017]:

- ~0% at age 35 years
- 50% at age 58 years
- Near 100% at age 80 years

## Anticipation

A decreasing age of onset in consecutive generations of family members heterozygous for a *C9orf72* $G_4C_2$ repeat expansion has been reported by some investigators [Van Mossevelde et al 2017b, Moore et al 2020] but not others [DeJesus-Hernandez et al 2011, Renton et al 2011, Barbier et al 2017]. Explanations for this discrepancy could include the following: (1) an apparent earlier age of onset due to observational or recall bias in families experienced with the disorder that prompted earlier medical attention and diagnosis; and (2) technical difficulties as well as age-related and tissue-related issues in correctly sizing the $G_4C_2$ repeat (see Molecular Genetics).

Thus, to date, $G_4C_2$ repeat size as measured in leukocyte DNA does not provide prognostic information, such as predicted presence or absence of clinical manifestations of *C9orf72*-FTD/ALS in an individual, or – if manifestations do develop – the age of onset or severity [Van Mossevelde et al 2017a].

## Prevalence

Detailed epidemiologic studies of the prevalence of the *C9orf72* $G_4C_2$ repeat expansion have not been performed. Based on the estimated prevalence of FTD and ALS in the general population and the frequency of a *C9orf72* $G_4C_2$ pathogenic repeat expansion in cohorts of individuals with FTD and ALS, the following rough estimates of *C9orf72*-FTD/ALS spectrum have been calculated.

- With the prevalence of FTD estimated at 1-461:100,000 [Hogan et al 2016] and with an average frequency of 4%-29% of *C9orf72* $G_4C_2$ repeat expansions in FTD cohorts [Van Mossevelde et al 2018], a rough estimate of *C9orf72*-FTD is 0.04-134:100,000.
- The prevalence of ALS is estimated at 5-12:100,000. Among individuals with ALS, about 10% have a family history consistent with autosomal dominant inheritance and about 90% have no family history of the disorder [Oskarsson et al 2018, Masrori & Van Damme 2020]. A pathogenic *C9orf72* G4C2 repeat expansion is observed on average in 30%-50% of individuals with familial ALS and 4%-10% of individuals with no family history of ALS [Majounie et al 2012b, Oskarsson et al 2018, Masrori & Van Damme 2020].

It is important to note that the frequency of *C9orf72* $G_4C_2$ repeat expansions greatly depends on ethnicity and geographic region.

- The highest repeat expansion frequencies are observed in individuals of northern European heritage.
- Markedly elevated expansion frequencies were reported in Scandinavian countries [Majounie et al 2012b, Lindquist et al 2013, van der Zee et al 2013, Smith et al 2013].
- By contrast, in Asian populations, expansion frequency is much lower [Majounie et al 2012b, Tsai et al 2012, Konno et al 2013, Zou et al 2013].

- Few studies have investigated the effect of repeat expansions in cohorts of African heritage [Nel et al 2019].

## Genetically Related (Allelic) Disorders

In the vast majority of individuals, *C9orf72* $G_4C_2$ pathogenic repeat expansions cause phenotypes within the *C9orf72*-FTD/ALS spectrum; however, increased susceptibility to phenotypic aspects of other neurodegenerative and psychiatric disorders has been reported [Van Mossevelde et al 2017a, Marogianni et al 2019].

## Differential Diagnosis

The frequency of *C9orf72* $G_4C_2$ repeat expansions significantly exceeds that of pathogenic variants in any other gene causing frontotemporal dementia (FTD) or amyotrophic lateral sclerosis (ALS).

**Family history.** The frequency of pathogenic *C9orf72* $G_4C_2$ repeat expansions is about twice as high in individuals with a family history of FTD and/or ALS compared to those without a family history of these disorders. A *C9orf72* $G_4C_2$ repeat expansion is found in:

- 25% of familial FTD;
- 30%-50% of familial ALS (Of note, only 10% of individuals with ALS have a positive family history and simplex cases [i.e., a single occurrence in a family] outnumber familial cases among individuals with *C9orf72*-ALS.);
- Up to 88% of individuals with manifestations of both FTD and ALS and a positive family history of these disorders [Cruts et al 2013, Masrori & Van Damme 2020].

**Differential diagnosis for *C9orf72*-FTD**

- **Other types of dementia, especially with behavioral changes.** Differential diagnosis includes "frontal variant" Alzheimer disease (see Alzheimer Disease Overview), diffuse Lewy body disease, Huntington disease, other forms of FTD (see *GRN* Frontotemporal Dementia), prion disease, corticobasal degeneration, and progressive supranuclear palsy.

  Some individuals with *C9orf72*-FTD/ALS have a choreiform movement disorder which (especially when combined with behavioral abnormalities) may be confused with Huntington disease (see Clinical Description, Atypical Presentations) [Hensman Moss et al 2014].

- **Psychiatric disorders.** Especially in *C9orf72*-bvFTD with prominent behavioral manifestations, often in young individuals, a psychiatric diagnosis such as depression, obsessive compulsive disorder, bipolar disorder, and schizophrenia may be considered. Diagnostic workup and longitudinal clinical follow up are likely to distinguish between psychiatric disorders and FTD; however, they may exist concomitantly.

  Age of onset of *C9orf72*-FTD (mean 58.2 years) was later than in *MAPT*-FTD (mean 49.5 years) and earlier than in *GRN*-FTD (mean 61.3 years) [Moore et al 2020]. Most studies report a similar onset age in individuals with *C9orf72*-FTD and those with FTD of unknown cause [Van Mossevelde et al 2018].

**Differential diagnosis for *C9orf72*-ALS**

- **Isolated upper motor signs.** Differential diagnosis includes compressive (cervical) myelopathy, hereditary spastic paraplegia, adrenomyeloneuropathy (see X-Linked Adrenoleukodystrophy), and cerebrotendinous xanthomatosis in individuals with isolated manifestations of upper motor involvement.
- **Lower motor signs.** Plexopathy, chronic inflammatory polyradiculoneuropathy, as well as multifocal motor, toxic, infectious, or metabolic neuropathies or myopathies including inclusion body myositis (see Inclusion Body Myopathy with Paget Disease of Bone and/or FTD) and polymyositis can mimic lower motor signs [Masrori & Van Damme 2020].

- **Other forms of upper and lower motor neuron disorders.** See ALS Overview, Differential Diagnosis.
- A rare ALS/FTD variant of **prion disease** [Vicente-Pascual et al 2018]

# Management

Consensus clinical management recommendations for *C9orf72* frontotemporal dementia and/or amyotrophic lateral sclerosis (*C9orf72*-FTD/ALS) have not been published.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *C9orf72*-FTD/ALS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 4.** Recommended Evaluations Following Initial Diagnosis in Individuals with *C9orf72*-FTD/ALS

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Neurologic** | Complete neurologic exam | Assess:<br>• UMN involvement: spasticity, Babinski signs, hyperreflexia;<br>• LMN involvement: weakness, amyotrophy, fasciculations; EMG. |
| **Cognitive function** | Neuropsychological exam | Evaluate extent & profile of cognitive disturbance. |
| **Musculoskeletal/ ADL** | Orthopedics / physical medicine & rehab / PT eval | To incl assessment of:<br>• Muscle tone, joint range of motion, posture, mobility, strength, coordination & endurance, pain, bedsores<br>• Need for adaptive devices<br>• Footwear needs<br>• PT needs<br>• Need for assistive walking devices (e.g., canes, walker, walker w/wheels, walker w/seat, wheelchairs) |
| | OT | Assess:<br>• Fine motor function, e.g., hands, feet, face, fingers, & toes;<br>• Home adaptations for ADL & safety. |
| | Eval of driving safety | In case of cognitive impairment & impaired judgment, evaluate driving safety. |
| **Psychiatric illness** | History of psychiatric illness [1] | • Attention to possible alcohol or drug abuse<br>• Referral for psychiatric eval as needed |
| **Dysarthria** | For those w/dysarthria: speech/language eval | Referral for speech therapy as needed |
| **Dysphagia** | For those w/frequent choking or severe dysphagia, assess:<br>• Nutritional status;<br>• Aspiration risk. | Consider involving a gastroenterology/nutrition/feeding team, incl formal swallowing eval. |
| **Respiratory function** | By pulmonologist | Assess respiratory function & need for respiratory support. |

*Table 4. continued from previous page.*

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Genetic counseling** | By genetics professionals [2] | To inform affected persons & their families re nature, MOI, & implications of *C9orf72*-FTD/ALS spectrum to facilitate medical & personal decision making |
| **Family support & resources** | Assess need for:<br>• Community or online resources such as Parent to Parent;<br>• Social work involvement for parental support;<br>• Home nursing referral. | • Early discussion of advanced care planning<br>• The affected person's perspective & burden must be considered in clinical decision making.<br>• The presence of cognitive impairment may raise ethical concerns. |

ADL = activities of daily living; EMG = electromyography; LMN = lower motor neuron; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; UMN = upper motor neuron

*1.* Devenney et al [2014], Piguet et al [2017], Oskarsson et al [2018], Masrori & Van Damme [2020]

*2.* Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

## Treatment of Manifestations

Many individuals benefit from care by a multidisciplinary team that includes a neurologist, specially trained nurses, pulmonologist, speech therapist, physical therapist, occupational therapist, respiratory therapist, nutritionist, psychologist, social worker, and genetic counselor.

For ALS-related treatment options, see also Amyotrophic Lateral Sclerosis Overview.

**Table 5.** Treatment of Manifestations in Individuals with *C9orf72*-FTD/ALS

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **UMN & LMN involvement / ADL** | • Physical medicine & rehab / PT & OT<br>• Riluzol<br>• Edaravone | • Ankle-foot braces, walkers, wheelchairs, hospital beds, toileting equipment, lifts to improve functionality<br>• Note: Edaravone is not approved worldwide. |
| **Spasticity** | Baclofen, tizanidine, cannabinoids, & muscle stretching | |
| **Muscle cramps** | Magnesium supplements, quinine sulfate, gabapentin, or carbamazepine | |
| **Parkinsonism** | PT, levodopa trial | Because of psychiatric levodopa side effects, use only when functional impairment is significant. |
| **Cognitive function** | Cognitive rehab | |
| **Psychiatric/ behavioral manifestations** | Environmental, behavioral, & physical interventions | To minimize occurrence & consequences of undesired behaviors |
| | Counseling | For those w/affective disorders or to support affected person &/or caretakers. |
| | SSRIs | For those w/affective disorders or disinhibition & challenging behaviors, the 1st-line approach is pharmacologic therapy. |
| | Venlafaxine | Used when apathy is prominent |
| | Atypical antipsychotics | • For severe manifestations (agitation, aggressiveness, psychosis) refractory to SSRIs<br>• Often a temporizing measure until affected person becomes more apathetic<br>• Note: Risk of iatrogenic extrapyramidal syndrome |

*Table 5. continued from previous page.*

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **Pseudobulbar affect** | Dextromethorphan/quinidine | |
| **Dysarthria** | Speech/language therapy | Use of augmentative communication devices |
| **Dysphagia** | Continuous eval & therapy | Safe swallowing techniques, diet modifications, gastrostomy tube |
| **Sialorrhea** | Anticholinergic medications, salivary gland botulinum toxin injections, or radiotherapy | Note: Anticholinergic medication can affect cognition. |
| **Respiratory function** | Assisted ventilation | Noninvasive at first, proceeding to tracheostomy if necessary |
| **Bladder dysfunction** | Anticholinergics & intravesical botulinum toxin | Note: Anticholinergic medication can affect cognition. |
| **Family/caregiver support & resources** | Psychosocial support & education via caregiver & patient support groups | To ↓ stress & burden on caregivers |

Based on Andersen et al [2012], Siuda et al [2014], Piguet et al [2017], Oskarsson et al [2018], and Masrori & Van Damme [2020]
ADL = activities of daily living; LMN = lower motor neuron; OT = occupational therapy; PT = physical therapy; SSRI = selective serotonin reuptake inhibitor; UMN = upper motor neuron

## Surveillance

**Table 6.** Recommended Surveillance for Individuals with *C9orf72*-FTD/ALS

| System/Concern | Evaluation | Frequency | |
|---|---|---|---|
| | | ALS | FTD |
| **Neurologic** | Neurologic exam for new manifestations &/or response to medications | Every 2-3 mos | Undefined; depends on disease progression & presenting symptoms |
| **Mobility/ADL** | Physical medicine & rehab / PT/OT | | |
| **Cognitive function** | Rapid screening tools, incl tests of verbal fluency | | |
| **Psychiatric/behavioral manifestations** | Medical history, neurologic exam | | |
| **Pseudobulbar affect** | Medical history | | Not applicable |
| **Dysarthria** | Eval by speech therapist | Every 3-6 mos | Undefined; depends on disease progression & presenting symptoms |
| **Dysphagia** | Medical history | Every 2-3 mos | Not applicable |
| **Sialorrhea** | | | |
| **Respiratory function** | Medical history, clinical exam, addl testing (e.g., forced vital capacity, vital capacity) | | |
| **Bladder function** | Medical history | | |
| **Family/caregiver support/ resources** | Medical history; assess need for addl support. | | Undefined; depends on disease progression & presenting symptoms |

Based on Andersen et al [2012], Piguet et al [2017]
ADL = activities of daily living; OT = occupational therapy; PT = physical therapy

## Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Although results in a preclinical setting only are available to date, antisense oligonucleotide therapy may be promising as a disease-modifying therapy in *C9orf72* repeat expansion heterozygotes. A Phase I clinical trial testing such an agent was commenced in 2018 (NCT03626012).

Other potential RNA therapies include the use of duplex and single-stranded small interfering RNAs to silence *C9orf72* transcripts, as well as adeno-associated virus-delivered artificial microRNAs targeting *C9orf72* [Panza et al 2020].

Promising results have been achieved in a Phase II/III clinical trial with the selective tyrosine kinase inhibitor masitinib, as an add-on therapy to riluzole in persons with ALS [Mora et al 2020]. An additional Phase III clinical trial to verify and further specify these effects is being set up (NCT03127267).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

*C9orf72* frontotemporal dementia and/or amyotrophic lateral sclerosis (*C9orf72*-FTD/ALS) is inherited in an autosomal dominant manner.

## Risk to Family Members

**Parents of a proband**

- To date, almost all individuals diagnosed with *C9orf72*-FTD/ALS inherited a *C9orf72* $G_4C_2$ repeat expansion from a heterozygous parent.

  In most families the heterozygous parent is affected; however, a heterozygous parent may not have clinical manifestations of the disorder due to age-dependent reduced penetrance (i.e., the parent may be too young to manifest the disorder) (see Penetrance).

- Molecular genetic testing is recommended for the parents of a proband who appears to be the only affected family member.

- If the *C9orf72* $G_4C_2$ repeat expansion is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo C9orf72* $G_4C_2$ repeat expansion. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism for a *C9orf72* $G_4C_2$ repeat expansion. (Testing of parental leukocyte DNA may not

detect all instances of somatic mosaicism.) Parental mosaicism for a *C9orf72* $G_4C_2$ repeat expansion has not been reported to date.

- The family history of some individuals with *C9orf72*-FTD/ALS may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for a *C9orf72* $G_4C_2$ repeat expansion.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have a *C9orf72* $G_4C_2$ repeat expansion, the risk to the sibs of inheriting the expansion is 50%.
- The clinical presentation of the *C9orf72*-FTD/ALS spectrum is highly heterogeneous and may differ between sibs who are heterozygous for the repeat expansion; whether – and at what age – manifestations will become apparent in a sib who inherits a *C9orf72* G4C2 repeat expansion cannot be predicted by the age of onset in other family members [Van Mossevelde et al 2017a].
- If both parents are clinically unaffected but their genetic status is unknown, sibs are still at increased risk for *C9orf72*-FTD/ALS because of the possibility of age-dependent reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

**Offspring of a proband.** Each child of an individual with *C9orf72*-FTD/ALS has a 50% chance of inheriting the *C9orf72* $G_4C_2$ repeat expansion.

**Other family members.** The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *C9orf72* $G_4C_2$ repeat expansion, the parent's family members may be at risk.

## Related Genetic Counseling Issues

**Predictive testing (i.e., testing of asymptomatic at-risk individuals)**

- Predictive testing for at-risk relatives is possible once the *C9orf72* $G_4C_2$ repeat expansion has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

**Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)**

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of *C9orf72*-FTD/ALS, it is appropriate to consider testing of symptomatic individuals regardless of age.

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

## Prenatal Testing and Preimplantation Genetic Testing

Once a *C9orf72* $G_4C_2$ repeat expansion has been identified in an affected family member, prenatal and preimplantation genetic testing for the presence of the *C9orf72* $G_4C_2$ repeat expansion are possible. (Note: The presence of a *C9orf72* $G_4C_2$ repeat expansion cannot predict the disease course in any given individual.)

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful. For more information, see the National Society of Genetic Counselors position statement on prenatal testing in adult-onset conditions.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **ALS Association**
  **Phone:** 800-782-4747
  **Email:** alsinfo@alsa-national.org
  www.alsa.org

- **Amyotrophic Lateral Sclerosis Society of Canada**
  Canada
  **Phone:** 800-267-4257 (toll-free); 416-497-2267
  **Email:** communityservices@als.ca
  www.als.ca

- **Association for Frontotemporal Degeneration (AFTD)**
  **Phone:** 866-507-7222
  **Email:** info@theaftd.org
  www.theaftd.org

- **International Alliance of ALS/MND Associations**
  1333 Race Street
  PO Box 40777
  Philadelphia PA 19107
  **Phone:** +1 215 568-2462
  **Fax:** +1 215 543-3366
  **Email:** alliance@als-mnd.org
  http://www.alsmndalliance.org

- **Les Turner ALS Foundation (Amyotrophic Lateral Sclerosis)**
  5550 West Touhy Avenue
  Suite 302
  Skokie IL 60077-3254
  **Phone:** 888-257-1107 (toll-free); 847-679-3311

**Fax:** 847-679-9109
**Email:** info@lesturnerals.org
www.lesturnerals.org

- **Rare Dementia Support**
  United Kingdom
  **Email:** contact@raredementiasupport.org
  www.raredementiasupport.org
- **ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration - Registry**
  www.allftd.org

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** C9orf72-Related Amyotrophic Lateral Sclerosis and/or Frontotemporal Dementia: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *C9orf72* | 9p21.2 | Guanine nucleotide exchange factor C9orf72 | alsod/C9orf72 genetic mutations | C9orf72 | C9orf72 |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for C9orf72-Related Amyotrophic Lateral Sclerosis and/or Frontotemporal Dementia (View All in OMIM)

| | |
|---|---|
| 105550 | FRONTOTEMPORAL DEMENTIA AND/OR AMYOTROPHIC LATERAL SCLEROSIS 1; FTDALS1 |
| 614260 | CHROMOSOME 9 OPEN READING FRAME 72; C9ORF72 |

## Molecular Pathogenesis

The $G_4C_2$ hexanucleotide repeat expansion is the only known pathogenic variant in *C9orf72* frontotemporal dementia and/or amyotrophic lateral sclerosis (*C9orf72*-FTD/ALS). There is currently no evidence that variants that alter the C9orf72 protein sequence are pathogenic.

**Mechanism of disease causation.** Although the molecular basis of *C9orf72*-FTD/ALS has been under intense investigation, the exact disease mechanism is not yet fully understood. Mounting evidence indicates the involvement of multiple disease mechanisms in a multiple-hit model of both gain-of-function and loss-of-function mechanisms:

- **Gain-of-function mechanisms**
  - RNA toxicity caused by sequestration of RNA-binding proteins and normal *C9orf72* transcripts by RNA species containing the pathogenic $G_4C_2$ (GGGGCC) hexanucleotide repeat expansion into nuclear RNA foci, thereby interfering with their physiologic functions [Mori et al 2013b]
  - $G_4C_2$ repeat-associated, non-ATG bidirectional translation of the expanded $G_4C_2$ hexanucleotide repeat sequences into diverse aggregation-prone dipeptide repeat (DPR) proteins (poly-GA, poly-GP, poly-GR, poly-PA, and poly-PR), leading to DPR-positive inclusion pathology [Mori et al 2013a, Mori et al 2013c]
- **Haploinsufficiency** due to loss of expression of *C9orf72* from the $G_4C_2$ expanded allele and reduced C9orf72 protein levels [Gijselinck et al 2012, van der Zee et al 2013, Braems et al 2020]

***C9orf72* technical considerations** (see Table 7). Accurate sizing of the $G_4C_2$ repeat expansion has proven cumbersome, complicating direct observation of expansion of the repeat and anticipation in large numbers of parent-offspring pairs. This is due to the 100% GC content, large size, somatic instability, and repetitive nature of its flanking sequences. Another barrier to accurately determining pathogenic repeat size is the difference in repeat length as measured in different tissues. As such, analysis on blood-derived DNA may not be a correct representation of the $G_4C_2$ repeat length in neuronal tissue. Reports have shown marked intraindividual differences in the repeat length between tissues, as well as a smaller variation in length within the same tissue [van Blitterswijk et al 2013, Nordin et al 2015, Gijselinck et al 2016]. Repeat length may also fluctuate during the lifetime of an individual, giving a significant correlation between repeat length and age at sample collection [Fournier et al 2019, Jackson et al 2020].

**Table 7.** *C9orf72* Technical Considerations

| Technical Issue | Comment [Reference] |
|---|---|
| **Sequence of repeat** | While it is plausible that repeat expansion producing thousands of repeat units could lead to imperfect replication & interruption of the pure $G_4C_2$ repeat sequence [Gao et al 2017], this has not been demonstrated to date owing to the difficulty of sequencing the *C9orf72* $G_4C_2$ repeat. |
| **Methods to detect expanded allele (See Table 8 .)** | Repeat-primed PCR (RP-PCR) & fragment length analysis [Gijselinck et al 2012], Southern blotting following pulse-field gel electrophoresis [Akimoto et al 2014]. Note: The Southern blotting methods for this repeat expansion require biomaterials, expertise, & equipment not commonly available in clinical labs. |
| **Somatic instability** | Alleles w/abnormal number of $G_4C_2$ repeats may display somatic instability of the repeat, appearing as "smeared" expanded alleles w/multiple distinct expansion alleles on PCR & Southern blot analyses [Gijselinck et al 2016]. |
| **Germline instability** | There is evidence that contraction of the repeat is primarily seen in paternal transmissions [Jackson et al 2020]. |

**Methods to characterize *C9orf72* $G_4C_2$ repeats.** Due to the technical challenges of detecting and sizing *C9orf72* $G_4C_2$ repeat expansions, multiple methods may be needed to rule out or detect $G_4C_2$ repeat expansion (see Table 8). Repeats in the normal range (2-24) may be detected by traditional PCR. However, detection of apparent homozygosity for a normal $G_4C_2$ repeat does not rule out the presence of an expanded $G_4C_2$ repeat; thus, testing by RP-PCR or Southern blotting is required. In addition, somatic and germline instability of expanded repeats must be considered.

**Table 8.** Methods to Characterize *C9orf72* $G_4C_2$ Repeats

| Interpretation of $G_4C_2$ Repeat Number | Expected Results by Method | | |
|---|---|---|---|
| | Conventional PCR | Repeat-primed PCR [1] | Expanded repeat analysis [2] |
| Normal: 2-24 [3] | Detected [4] | See footnote 1. | Expansions can be detected & repeat size can be approximated. [5, 6] |
| Intermediate: 25-60 [3] | | Expansions may be detected but repeat size cannot be determined. [7, 8] | |
| Pathogenic: 61->4,000 | Detected up to ~80 repeats [4, 9] | Expansions are detected but repeat size cannot be determined. [8] | |

*1.* The design of an RP-PCR assay may include conventional PCR primers to size normal repeats and detect expanded repeats in a single assay. The RP-PCR assay itself does not determine repeat size – even alleles in the normal range.
*2.* Methods to detect and approximate the size of expanded repeats include long-range PCR sized by gel electrophoresis and Southern blotting. The upper limit of repeat size detected will vary by assay design, laboratory, sample, and/or patient due to competition by the normal allele during amplification. Further improvements in single-molecule long-read DNA sequencing technologies will allow more accurate sizing of the repeat and unravel possible interruptions in the repeat sequence, which may influence its stability, pathogenicity, and clinical manifestation [Gijselinck et al 2018].
*3.* The smallest unstable repeat reported is ~50 $G_4C_2$ repeats [Gijselinck et al 2016].
*4.* Detection of an apparently homozygous repeat does not rule out the presence of an expanded $G_4C_2$ repeat; thus, testing by RP-PCR or expanded repeat analysis is required to detect a repeat expansion.
*5.* Southern blotting for the $G_4C_2$ repeat expansion has been described [Akimoto et al 2014].
*6.* Precise sizing of repeats is not necessary as clinical utility for determining the exact repeat number has not been demonstrated.
*7.* RP-PCR for the $G_4C_2$ repeat expansion has been described [Gijselinck et al 2012, van der Zee et al 2013, Gijselinck et al 2016].
*8.* Repeats at the lower end of this range may not show the characteristic stutter pattern that indicates an expanded repeat.
*9.* The upper limit of repeat size detected will vary by assay design, laboratory, sample, and/or patient due to competition by the normal allele during amplification.

**Table 9.** Notable *C9orf72* Variants

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Repeat Range |
|---|---|---|---|
| NM_145005.6 | c.-45+258_-45+263delGGGGCC[2_24] | -- | Normal |
| | c.-45+258_-45+263delGGGGCC[25_60] | -- | Of uncertain significance |
| | c.-45+258_-45+263delGGGGCC[61_>4000] | -- | Pathogenic w/age-dependent reduced penetrance |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

# Chapter Notes

## Author Notes

The Neurodegenerative Brain Diseases group investigates the molecular mechanisms underlying neurodegenerative dementias and related disorders. We identify novel key proteins in neurodegeneration as potential targets for early diagnosis, risk prediction, and drug and biomarker development. Concurrently, we study the post-genomic consequences of disease-related genetic defects to improve our knowledge of the molecular mechanisms underlying these brain diseases and accelerate the development of more effective

treatments. The expertise of the group is in genetics, genomics and functional genomics of Alzheimer disease, frontotemporal lobar degeneration, dementia with Lewy bodies, and Parkinson disease.

VIB Center for Molecular Neurology

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# References

## Published Guidelines / Consensus Statements

- Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 12-29-22.
- National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 12-29-22.

## Literature Cited

Akimoto C, Volk AE, van Blitterswijk M, Van den Broeck M, Leblond CS, Lumbroso S, Camu W, Neitzel B, Onodera O, van Rheenen W, Pinto S, Weber M, Smith B, Proven M, Talbot K, Keagle P, Chesi A, Ratti A, van der Zee J, Alstermark H, Birve A, Calini D, Nordin A, Tradowsky DC, Just W, Daoud H, Angerbauer S, DeJesus-Hernandez M, Konno T, Lloyd-Jani A, de Carvalho M, Mouzat K, Landers JE, Veldink JH, Silani V, Gitler AD, Shaw CE, Rouleau GA, van den Berg LH, Van Broeckhoven C, Rademakers R, Andersen PM, Kubisch C. A blinded international study on the reliability of genetic testing for GGGGCC-repeat expansions in C9orf72 reveals marked differences in results among 14 laboratories. J Med Genet. 2014;51:419–24. PubMed PMID: 24706941.

Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Van Damme P, Hardiman O, Kollewe K, Morrison KE, Petri S, Pradat PF, Silani V, Tomik B, Wasner M, Weber M, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. Eur J Neurol. 2012;19:360–75. PubMed PMID: 21914052.

Barbier M, Camuzat A, Houot M, Clot F, Caroppo P, Fournier C, Rinaldi D, Pasquier F, Hannequin D, Pariente J, Larcher K, Brice A, Génin E, Sabbagh A, Le Ber I, et al. Factors influencing the age at onset in familial frontotemporal lobar dementia: Important weight of genetics. Neurol Genet. 2017;3:e203. PubMed PMID: 29264395.

Beck J, Poulter M, Hensman D, Rohrer JD, Mahoney CJ, Adamson G, Campbell T, Uphill J, Borg A, Fratta P, Orrell RW, Malaspina A, Rowe J, Brown J, Hodges J, Sidle K, Polke JM, Houlden H, Schott JM, Fox NC, Rossor MN, Tabrizi SJ, Isaacs AM, Hardy J, Warren JD, Collinge J, Mead S. Large C9orf72 hexanucleotide repeat expansions are seen in multiple neurodegenerative syndromes and are more frequent than expected in the UK population. Am J Hum Genet. 2013;92:345–53. PubMed PMID: 23434116.

Benussi L, Rossi G, Glionna M, Tonoli E, Piccoli E, Fostinelli S, Paterlini A, Flocco R, Albani D, Pantieri R, Cereda C, Forloni G, Tagliavini F, Binetti G, Ghidoni R. C9ORF72 hexanucleotide repeat number in frontotemporal lobar degeneration: a genotype-phenotype correlation study. J Alzheimers Dis. 2015;45:319. PubMed PMID: 25737153.

Bieniek KF, van Blitterswijk M, Baker MC, Petrucelli L, Rademakers R, Dickson DW. Expanded C9ORF72 hexanucleotide repeat in depressive pseudodementia. JAMA Neurol. 2014;71:775–81. PubMed PMID: 24756204.

Bourinaris T, Houlden H. C9orf72 and its relevance in parkinsonism and movement disorders: a comprehensive review of the literature. Mov Disord Clin Pract. 2018;5:575–85. PubMed PMID: 30637277.

Braems E, Swinnen B, Van Den Bosch L. C9orf72 loss-of-function: a trivial, stand-alone or additive mechanism in C9 ALS/FTD? Acta Neuropathol. 2020;140:625–43. PubMed PMID: 32876811.

Cacace R, Van Cauwenberghe C, Bettens K, Gijselinck I, van der Zee J, Engelborghs S, Vandenbulcke M, Van Dongen J, Bäumer V, Dillen L, Mattheijssens M, Peeters K, Cruts M, Vandenberghe R, De Deyn PP, Van Broeckhoven C, Sleegers K. C9orf72 G4C2 repeat expansions in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging. 2013;34:1712.e1–7.

Cali CP, Patino M, Tai YK, Ho WY, McLean CA, Morris CM, Seeley WW, Miller BL, Gaig C, Vonsattel JPG, White CL 3rd, Roeber S, Kretzschmar H, Troncoso JC, Troakes C, Gearing M, Ghetti B, Van Deerlin VM, Lee VM, Trojanowski JQ, Mok KY, Ling H, Dickson DW, Schellenberg GD, Ling SC, Lee EB. C9orf72 intermediate repeats are associated with corticobasal degeneration, increased C9orf72 expression and disruption of autophagy. Acta Neuropathol. 2019;138:795–811. PubMed PMID: 31327044.

Cammack AJ, Atassi N, Hyman T, van den Berg LH, Harms M, Baloh RH, Brown RH, van Es MA, Veldink JH, de Vries BS, Rothstein JD, Drain C, Jockel-Balsarotti J, Malcolm A, Boodram S, Salter A, Wightman N, Yu H, Sherman AV, Esparza TJ, McKenna-Yasek D, Owegi MA, Douthwright C. Alzheimer's Disease Neuroimaging Initiative, McCampbell A, Ferguson T, Cruchaga C, Cudkowicz M, Miller TM. Prospective natural history study of C9orf72 ALS clinical characteristics and biomarkers. Neurology. 2019;93:e1605–e1617. PubMed PMID: 31578300.

Cash DM, Bocchetta M, Thomas DL, Dick KM, van Swieten JC, Borroni B, Galimberti D, Masellis M, Tartaglia MC, Rowe JB, Graff C, Tagliavini F, Frisoni GB, Laforce R Jr, Finger E, de Mendonça A, Sorbi S, Rossor MN, Ourselin S, Rohrer JD, et al. Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. Neurobiol Aging. 2018;62:191–6. PubMed PMID: 29172163.

Cooper-Knock J, Higginbottom A, Connor-Robson N, Bayatti N, Bury JJ, Kirby J, Ninkina N, Buchman VL, Shaw PJ. C9ORF72 transcription in a frontotemporal dementia case with two expanded alleles. Neurology. 2013;81:1719–21. PubMed PMID: 24107864.

Cruts M, Gijselinck I, Van Langenhove T, van der Zee J, Van Broeckhoven C. Current insights into the C9orf72 repeat expansion diseases of the FTLD/ALS spectrum. Trends Neurosci. 2013;36:450–9. PubMed PMID: 23746459.

DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, Nicholson AM, Finch NA, Flynn H, Adamson J, Kouri N, Wojtas A, Sengdy P, Hsiung GY, Karydas A, Seeley WW, Josephs KA, Coppola G, Geschwind DH, Wszolek ZK, Feldman H, Knopman DS, Petersen RC, Miller BL, Dickson DW, Boylan KB, Graff-Radford NR, Rademakers R. Expanded GGGGCC hexanucleotide repeat in noncoding region of

C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011;72:245–56. PubMed PMID: 21944778.

Devenney E, Hornberger M, Irish M, Mioshi E, Burrell J, Tan R, Kiernan MC, Hodges JR. Frontotemporal dementia associated with the C9ORF72 mutation: a unique clinical profile. JAMA Neurol. 2014;71:331–9. PubMed PMID: 24445580.

Dobson-Stone C, Hallupp M, Bartley L, Shepherd CE, Halliday GM, Schofield PR, Hodges JR, Kwok JB. C9ORF72 repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts. Neurology. 2012;79:995–1001. PubMed PMID: 22875086.

Fournier C, Barbier M, Camuzat A, Anquetil V, Lattante S, Clot F, Cazeneuve C, Rinaldi D, Couratier P, Deramecourt V, Sabatelli M, Belliard S, Vercelletto M, Forlani S, Jornea L, Leguern E, Brice A, Le Ber I, et al. Relations between C9orf72 expansion size in blood, age at onset, age at collection and transmission across generations in patients and presymptomatic carriers. Neurobiol Aging. 2019;74:234.e1–234.e8.

Fratta P, Poulter M, Lashley T, Rohrer JD, Polke JM, Beck J, Ryan N, Hensman D, Mizielinska S, Waite AJ, Lai MC, Gendron TF, Petrucelli L, Fisher EM, Revesz T, Warren JD, Collinge J, Isaacs AM, Mead S. Homozygosity for the C9orf72 GGGGCC repeat expansion in frontotemporal dementia. Acta Neuropathol. 2013;126:401–9. PubMed PMID: 23818065.

Gao FB, Richter JD, Cleveland DW. Rethinking unconventional translation in neurodegeneration. Cell. 2017;171:994–1000. PubMed PMID: 29149615.

Gijselinck I, Cruts M, Van Broeckhoven C. The genetics of C9orf72 expansions. Cold Spring Harb Perspect Med. 2018;8:a026757. PubMed PMID: 28130313.

Gijselinck I, Van Langenhove T, van der Zee J, Sleegers K, Philtjens S, Kleinberger G, Janssens J, Bettens K, Van Cauwenberghe C, Pereson S, Engelborghs S, Sieben A, De Jonghe P, Vandenberghe R, Santens P, De Bleecker J, Maes G, Bäumer V, Dillen L, Joris G, Cuijt I, Corsmit E, Elinck E, Van Dongen J, Vermeulen S, Van den Broeck M, Vaerenberg C, Mattheijssens M, Peeters K, Robberecht W, Cras P, Martin JJ, De Deyn PP, Cruts M, Van Broeckhoven C. A. C9orf72 promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study. Lancet Neurol. 2012;11:54–65. PubMed PMID: 22154785.

Gijselinck I, Van Mossevelde S, van der Zee J, Sieben A, Engelborghs S, De Bleecker J, Ivanoiu A, Deryck O, Edbauer D, Zhang M, Heeman B, Bäumer V, Van den Broeck M, Mattheijssens M, Peeters K, Rogaeva E, De Jonghe P, Cras P, Martin JJ, de Deyn PP, Cruts M, Van Broeckhoven C. The C9orf72 repeat size correlates with onset age of disease, DNA methylation and transcriptional downregulation of the promoter. Mol Psychiatry. 2016;21:1112–24. PubMed PMID: 26481318.

Greaves CV, Rohrer JD. An update on genetic frontotemporal dementia. J Neurol. 2019;266:2075–86. PubMed PMID: 31119452.

Harms M, Benitez BA, Cairns N, Cooper B, Cooper P, Mayo K, Carrell D, Faber K, Williamson J, Bird T, Diaz-Arrastia R, Foroud TM, Boeve BF, Graff-Radford NR, Mayeux R, Chakraverty S, Goate AM, Cruchaga C, et al. C9orf72 hexanucleotide repeat expansions in clinical Alzheimer disease. JAMA Neurol. 2013;70:736–41. PubMed PMID: 23588422.

Hensman Moss DJ, Poulter M, Beck J, Hehir J, Polke JM, Campbell T, Adamson G, Mudanohwo E, McColgan P, Haworth A, Wild EJ, Sweeney MG, Houlden H, Mead S, Tabrizi SJ. C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. Neurology. 2014;82:292–9. PubMed PMID: 24363131.

Hogan DB, Jetté N, Fiest KM, Roberts JI, Pearson D, Smith EE, Roach P, Kirk A, Pringsheim T, Maxwell CJ. The prevalence and incidence of frontotemporal dementia: a systematic review. Can J Neurol Sci. 2016;43 Suppl 1:S96–S109. PubMed PMID: 27307130.

Jackson JL, Finch NA, Baker MC, Kachergus JM, DeJesus-Hernandez M, Pereira K, Christopher E, Prudencio M, Heckman MG, Thompson EA, Dickson DW, Shah J, Oskarsson B, Petrucelli L, Rademakers R, van Blitterswijk M. Elevated methylation levels, reduced expression levels, and frequent contractions in a clinical cohort of C9orf72 expansion carriers. Mol Neurodegener. 2020;15:7. PubMed PMID: 32000838.

Kohli MA, John-Williams K, Rajbhandary R, Naj A, Whitehead P, Hamilton K, Carney RM, Wright C, Crocco E, Gwirtzman HE, Lang R, Beecham G, Martin ER, Gilbert J, Benatar M, Small GW, Mash D, Byrd G, Haines JL, Pericak-Vance MA, Züchner S. Repeat expansions in the C9ORF72 gene contribute to Alzheimer's disease in Caucasians. Neurobiol Aging. 2013;34:1519.e5–12.

Konno T, Shiga A, Tsujino A, Sugai A, Kato T, Kanai K, Yokoseki A, Eguchi H, Kuwabara S, Nishizawa M, Takahashi H, Onodera O. Japanese amyotrophic lateral sclerosis patients with GGGGCC hexanucleotide repeat expansion in C9ORF72. J Neurol Neurosurg Psychiatry. 2013;84:398–401. PubMed PMID: 23012445.

Lesage S, Le Ber I, Condroyer C, Broussolle E, Gabelle A, Thobois S, Pasquier F, Mondon K, Dion PA, Rochefort D, Rouleau GA, Dürr A, Brice A, et al. C9orf72 repeat expansions are a rare genetic cause of parkinsonism. Brain. 2013;136(Pt 2):385–91. PubMed PMID: 23413259.

Lindquist SG, Duno M, Batbayli M, Puschmann A, Braendgaard H, Mardosiene S, Svenstrup K, Pinborg LH, Vestergaard K, Hjermind LE, Stokholm J, Andersen BB, Johannsen P, Nielsen JE. Corticobasal and ataxia syndromes widen the spectrum of C9ORF72 hexanucleotide expansion disease. Clin Genet. 2013;83:279–83. PubMed PMID: 22650353.

Majounie E, Abramzon Y, Renton AE, Perry R, Bassett SS, Pletnikova O, Troncoso JC, Hardy J, Singleton AB, Traynor BJ. Repeat expansion in C9ORF72 in Alzheimer's disease. N Engl J Med. 2012a;366:283–4. PubMed PMID: 22216764.

Majounie E, Renton AE, Mok K, Dopper EG, Waite A, Rollinson S, Chiò A, Restagno G, Nicolaou N, Simon-Sanchez J, van Swieten JC, Abramzon Y, Johnson JO, Sendtner M, Pamphlett R, Orrell RW, Mead S, Sidle KC, Houlden H, Rohrer JD, Morrison KE, Pall H, Talbot K, Ansorge O, Hernandez DG, Arepalli S, Sabatelli M, Mora G, Corbo M, Giannini F, Calvo A, Englund E, Borghero G, Floris GL, Remes AM, Laaksovirta H, McCluskey L, Trojanowski JQ, Van Deerlin VM, Schellenberg GD, Nalls MA, Drory VE, Lu CS, Yeh TH, Ishiura H, Takahashi Y, Tsuji S, Le Ber I, Brice A, Drepper C, Williams N, Kirby J, Shaw P, Hardy J, Tienari PJ, Heutink P, Morris HR, Pickering-Brown S, Traynor BJ, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012b;11:323–30. PubMed PMID: 22406228.

Marogianni C, Rikos D, Provatas A, Dadouli K, Ntellas P, Tsitsi P, Patrinos G, Dardiotis E, Hadjigeorgiou G, Xiromerisiou G. The role of C9orf72 in neurodegenerative disorders: a systematic review, an updated meta-analysis, and the creation of an online database. Neurobiol Aging. 2019;84:238.e25–238.e34.

Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020;27:1918–29. PubMed PMID: 32526057.

Moore KM, Nicholas J, Grossman M, McMillan CT, Irwin DJ, Massimo L, Van Deerlin VM, Warren JD, Fox NC, Rossor MN, Mead S, Bocchetta M, Boeve BF, Knopman DS, Graff-Radford NR, Forsberg LK, Rademakers R, Wszolek ZK, van Swieten JC, Jiskoot LC, Meeter LH, Dopper EG, Papma JM, Snowden JS, Saxon J, Jones M, Pickering-Brown S, Le Ber I, Camuzat A, Brice A, Caroppo P, Ghidoni R, Pievani M, Benussi L, Binetti G, Dickerson BC, Lucente D, Krivensky S, Graff C, Öijerstedt L, Fallström M, Thonberg H, Ghoshal N, Morris JC, Borroni B, Benussi A, Padovani A, Galimberti D, Scarpini E, Fumagalli GG, Mackenzie IR, Hsiung GR, Sengdy P, Boxer AL, Rosen H, Taylor JB, Synofzik M, Wilke C, Sulzer P, Hodges JR, Halliday G, Kwok J, Sanchez-Valle R, Lladó A, Borrego-Ecija S, Santana I, Almeida MR, Tábuas-Pereira M, Moreno F, Barandiaran M, Indakoetxea B, Levin J, Danek A, Rowe JB, Cope TE, Otto M, Anderl-Straub S, de Mendonça A, Maruta C, Masellis M, Black SE, Couratier P, Lautrette G, Huey ED, Sorbi S, Nacmias B, Laforce R Jr, Tremblay ML, Vandenberghe R, Damme PV, Rogalski EJ, Weintraub S, Gerhard A, Onyike CU, Ducharme S, Papageorgiou SG, Ng ASL, Brodtmann A, Finger E, Guerreiro R, Bras J, Rohrer JD, et al. Age at

symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. Lancet Neurol. 2020;19:145–56. PubMed PMID: 31810826.

Mora JS, Genge A, Chio A, Estol CJ, Chaverri D, Hernández M, Marín S, Mascias J, Rodriguez GE, Povedano M, Paipa A, Dominguez R, Gamez J, Salvado M, Lunetta C, Ballario C, Riva N, Mandrioli J, Moussy A, Kinet JP, Auclair C, Dubreuil P, Arnold V, Mansfield CD, Hermine O, et al. Masitinib as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomized clinical trial. Amyotroph Lateral Scler Frontotemporal Degener. 2020;21:5–14. PubMed PMID: 31280619.

Mori K, Arzberger T, Grässer FA, Gijselinck I, May S, Rentzsch K, Weng SM, Schludi MH, van der Zee J, Cruts M, Van Broeckhoven C, Kremmer E, Kretzschmar HA, Haass C, Edbauer D. Bidirectional transcripts of the expanded C9orf72 hexanucleotide repeat are translated into aggregating dipeptide repeat proteins. Acta Neuropathol. 2013a;126:881–93. PubMed PMID: 24132570.

Mori K, Lammich S, Mackenzie IR, Forné I, Zilow S, Kretzschmar H, Edbauer D, Janssens J, Kleinberger G, Cruts M, Herms J, Neumann M, Van Broeckhoven C, Arzberger T, Haass C. hnRNP A3 binds to GGGGCC repeats and is a constituent of p62-positive/TDP43-negative inclusions in the hippocampus of patients with C9orf72 mutations. Acta Neuropathol. 2013b;125:413–23. PubMed PMID: 23381195.

Mori K, Weng SM, Arzberger T, May S, Rentzsch K, Kremmer E, Schmid B, Kretzschmar HA, Cruts M, Van Broeckhoven C, Haass C, Edbauer D. The C9orf72 GGGGCC repeat is translated into aggregating dipeptide-repeat proteins in FTLD/ALS. Science. 2013c;339:1335–8. PubMed PMID: 23393093.

Murphy NA, Arthur KC, Tienari PJ, Houlden H, Chiò A, Traynor BJ. Age-related penetrance of the C9orf72 repeat expansion. Sci Rep. 2017;7:2116. PubMed PMID: 28522837.

Murray ME, DeJesus-Hernandez M, Rutherford NJ, Baker M, Duara R, Graff-Radford NR, Wszolek ZK, Ferman TJ, Josephs KA, Boylan KB, Rademakers R, Dickson DW. Clinical and neuropathologic heterogeneity of c9FTD/ALS associated with hexanucleotide repeat expansion in C9ORF72. Acta Neuropathol. 2011;122:673–90. PubMed PMID: 22083254.

Nel M, Agenbag GM, Henning F, Cross HM, Esterhuizen A, Heckmann JM. C9orf72 repeat expansions in South Africans with amyotrophic lateral sclerosis. J Neurol Sci. 2019;401:51–4. PubMed PMID: 31009932.

Niemantsverdriet E, Feyen BFE, Le Bastard N, Martin JJ, Goeman J, De Deyn PP, Bjerke M, Engelborghs S. Added diagnostic value of cerebrospinal fluid biomarkers for differential dementia diagnosis in an autopsy-confirmed cohort. J Alzheimers Dis. 2018;63:373–81. PubMed PMID: 29614653.

Nordin A, Akimoto C, Wuolikainen A, Alstermark H, Jonsson P, Birve A, Marklund SL, Graffmo KS, Forsberg K, Brännström T, Andersen PM. Extensive size variability of the GGGGCC expansion in C9orf72 in both neuronal and non-neuronal tissues in 18 patients with ALS or FTD. Hum Mol Genet. 2015;24:3133–42. PubMed PMID: 25712133.

Oskarsson B, Gendron TF, Staff NP. Amyotrophic lateral sclerosis: an update for 2018. Mayo Clin Proc. 2018;93:1617–28. PubMed PMID: 30401437.

Panza F, Lozupone M, Seripa D, Daniele A, Watling M, Giannelli G, Imbimbo BP. Development of disease-modifying drugs for frontotemporal dementia spectrum disorders. Nat Rev Neurol. 2020;16:213–28. PubMed PMID: 32203398.

Piguet O, Kumfor F, Hodges J. Diagnosing, monitoring and managing behavioural variant frontotemporal dementia. Med J Aust. 2017;207:303–8. PubMed PMID: 28954617.

Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, Schymick JC, Laaksovirta H, van Swieten JC, Myllykangas L, Kalimo H, Paetau A, Abramzon Y, Remes AM, Kaganovich A, Scholz SW, Duckworth J, Ding J, Harmer DW, Hernandez DG, Johnson JO, Mok K, Ryten M, Trabzuni D, Guerreiro RJ, Orrell RW, Neal J, Murray A, Pearson J, Jansen IE, Sondervan D, Seelaar H, Blake D, Young K, Halliwell N, Callister JB, Toulson G, Richardson A, Gerhard A, Snowden J, Mann D, Neary D, Nalls MA, Peuralinna T, Jansson L, Isoviita VM, Kaivorinne AL, Hölttä-Vuori M, Ikonen E, Sulkava R, Benatar M, Wuu J, Chiò A,

Restagno G, Borghero G, Sabatelli M; ITALSGEN Consortium. Heckerman D, Rogaeva E, Zinman L, Rothstein JD, Sendtner M, Drepper C, Eichler EE, Alkan C, Abdullaev Z, Pack SD, Dutra A, Pak E, Hardy J, Singleton A, Williams NM, Heutink P, Pickering-Brown S, Morris HR, Tienari PJ, Traynor BJ. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011;72:257–68. PubMed PMID: 21944779.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Schottlaender LV, Polke JM, Ling H, MacDoanld ND, Tucci A, Nanji T, Pittman A, de Silva R, Holton JL, Revesz T, Sweeney MG, Singleton AB, Lees AJ, Bhatia KP, Houlden H. Analysis of C9orf72 repeat expansions in a large series of clinically and pathologically diagnosed cases with atypical parkinsonism. Neurobiol Aging. 2015;36:1221.e1–6.

Siuda J, Fujioka S, Wszolek ZK. Parkinsonian syndrome in familial frontotemporal dementia. Parkinsonism Relat Disord. 2014;20:957–64. PubMed PMID: 24998994.

Smith BN, Newhouse S, Shatunov A, Vance C, Topp S, Johnson L, Miller J, Lee Y, Troakes C, Scott KM, Jones A, Gray I, Wright J, Hortobágyi T, Al-Sarraj S, Rogelj B, Powell J, Lupton M, Lovestone S, Sapp PC, Weber M, Nestor PJ, Schelhaas HJ, Asbroek AA, Silani V, Gellera C, Taroni F, Ticozzi N, Van den Berg L, Veldink J, Van Damme P, Robberecht W, Shaw PJ, Kirby J, Pall H, Morrison KE, Morris A, de Belleroche J, Vianney de Jong JM, Baas F, Andersen PM, Landers J, Brown RH Jr, Weale ME, Al-Chalabi A, Shaw CE. The C9ORF72 expansion mutation is a common cause of ALS+/-FTD in Europe and has a single founder. Eur J Hum Genet. 2013;21:102–8. PubMed PMID: 22692064.

Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, Jones M, Gerhard A, Davidson YS, Robinson A, Gibbons L, Hu Q, DuPlessis D, Neary D, Mann DM, Pickering-Brown SM. Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. Brain. 2012;135:693–708. PubMed PMID: 22300873.

Theuns J, Verstraeten A, Sleegers K, Wauters E, Gijselinck I, Smolders S, Crosiers D, Corsmit E, Elinck E, Sharma M, Krüger R, Lesage S, Brice A, Chung SJ, Kim MJ, Kim YJ, Ross OA, Wszolek ZK, Rogaeva E, Xi Z, Lang AE, Klein C, Weissbach A, Mellick GD, Silburn PA, Hadjigeorgiou GM, Dardiotis E, Hattori N, Ogaki K, Tan EK, Zhao Y, Aasly J, Valente EM, Petrucci S, Annesi G, Quattrone A, Ferrarese C, Brighina L, Deutschländer A, Puschmann A, Nilsson C, Garraux G, LeDoux MS, Pfeiffer RF, Boczarska-Jedynak M, Opala G, Maraganore DM, Engelborghs S, De Deyn PP, Cras P, Cruts M, Van Broeckhoven C, et al. Global investigation and meta-analysis of the C9orf72 (G4C2)n repeat in Parkinson disease. Neurology. 2014;83:1906–13. PubMed PMID: 25326098.

Tsai CP, Soong BW, Tu PH, Lin KP, Fuh JL, Tsai PC, Lu YC, Lee IH, Lee YC. A hexanucleotide repeat expansion in C9ORF72 causes familial and sporadic ALS in Taiwan. Neurobiol Aging. 2012;33:2232.e11–2232.e18.

van Blitterswijk M, DeJesus-Hernandez M, Niemantsverdriet E, Murray ME, Heckman MG, Diehl NN, Brown PH, Baker MC, Finch NA, Bauer PO, Serrano G, Beach TG, Josephs KA, Knopman DS, Petersen RC, Boeve BF, Graff-Radford NR, Boylan KB, Petrucelli L, Dickson DW, Rademakers R. Association between repeat sizes and clinical and pathological characteristics in carriers of C9ORF72 repeat expansions (Xpansize-72): a cross-sectional cohort study. Lancet Neurol. 2013;12:978–88. PubMed PMID: 24011653.

van der Zee J, Gijselinck I, Dillen L, Van Langenhove T, Theuns J, Engelborghs S, Philtjens S, Vandenbulcke M, Sleegers K, Sieben A, Bäumer V, Maes G, Corsmit E, Borroni B, Padovani A, Archetti S, Perneczky R, Diehl-Schmid J, de Mendonça A, Miltenberger-Miltenyi G, Pereira S, Pimentel J, Nacmias B, Bagnoli S, Sorbi S, Graff C, Chiang HH, Westerlund M, Sanchez-Valle R, Llado A, Gelpi E, Santana I, Almeida MR, Santiago B, Frisoni G, Zanetti O, Bonvicini C, Synofzik M, Maetzler W, Vom Hagen JM, Schöls L, Heneka MT, Jessen F, Matej R, Parobkova E, Kovacs GG, Ströbel T, Sarafov S, Tournev I, Jordanova A, Danek A, Arzberger T,

Fabrizi GM, Testi S, Salmon E, Santens P, Martin JJ, Cras P, Vandenberghe R, De Deyn PP, Cruts M, Van Broeckhoven C, van der Zee J, Gijselinck I, Dillen L, Van Langenhove T, Theuns J, Philtjens S, Sleegers K, Bäumer V, Maes G, Corsmit E, Cruts M, Van Broeckhoven C, van der Zee J, Gijselinck I, Dillen L, Van Langenhove T, Philtjens S, Theuns J, Sleegers K, Bäumer V, Maes G, Cruts M, Van Broeckhoven C, Engelborghs S, De Deyn PP, Cras P, Engelborghs S, De Deyn PP, Vandenbulcke M, Vandenbulcke M, Borroni B, Padovani A, Archetti S, Perneczky R, Diehl-Schmid J, Synofzik M, Maetzler W, Müller Vom Hagen J, Schöls L, Synofzik M, Maetzler W, Müller Vom Hagen J, Schöls L, Heneka MT, Jessen F, Ramirez A, Kurzwelly D, Sachtleben C, Mairer W, de Mendonça A, Miltenberger-Miltenyi G, Pereira S, Firmo C, Pimentel J, Sanchez-Valle R, Llado A, Antonell A, Molinuevo J, Gelpi E, Graff C, Chiang HH, Westerlund M, Graff C, Kinhult Ståhlbom A, Thonberg H, Nennesmo I, Börjesson-Hanson A, Nacmias B, Bagnoli S, Sorbi S, Bessi V, Piaceri I, Santana I, Santiago B, Santana I, Helena Ribeiro M, Rosário Almeida M, Oliveira C, Massano J, Garret C, Pires P, Frisoni G, Zanetti O, Bonvicini C, Sarafov S, Tournev I, Jordanova A, Tournev I, Kovacs GG, Ströbel T, Heneka MT, Jessen F, Ramirez A, Kurzwelly D, Sachtleben C, Mairer W, Jessen F, Matej R, Parobkova E, Danel A, Arzberger T, Maria Fabrizi G, Testi S, Ferrari S, Cavallaro T, Salmon E, Santens P, Cras P, et al. A pan-European study of the C9orf72 repeat associated with FTLD: geographic prevalence, genomic instability, and intermediate repeats. Hum Mutat. 2013;34:363–73. PubMed PMID: 23111906.

Van Mossevelde S, Engelborghs S, van der Zee J, Van Broeckhoven C. Genotype-phenotype links in frontotemporal lobar degeneration. Nat Rev Neurol. 2018;14:363–78. PubMed PMID: 29777184.

Van Mossevelde S, van der Zee J, Cruts M, Van Broeckhoven C. Relationship between C9orf72 repeat size and clinical phenotype. Curr Opin Genet Dev. 2017a;44:117–24. PubMed PMID: 28319737.

Van Mossevelde S, van der Zee J, Gijselinck I, Sleegers K, De Bleecker J, Sieben A, Vandenberghe R, Van Langenhove T, Baets J, Deryck O, Santens P, Ivanoiu A, Willems C, Bäumer V, Van den Broeck M, Peeters K, Mattheijssens M, De Jonghe P, Cras P, Martin JJ, Cruts M, De Deyn PP, Engelborghs S, Van Broeckhoven C, et al. Clinical evidence of disease anticipation in families segregating a C9orf72 repeat expansion. JAMA Neurol. 2017b;74:445–52. PubMed PMID: 28192553.

Vicente-Pascual M, Rossi M, Gámez J, Lladó A, Valls J, Grau-Rivera O, Ávila Polo R, Llorens F, Zerr I, Ferrer I, Nos C, Parchi P, Sánchez-Valle R, Gelpí E. Variably protease-sensitive prionopathy presenting within ALS/FTD spectrum. Ann Clin Transl Neurol. 2018;5:1297–1302. PubMed PMID: 30349865.

Wilke C, Pomper JK, Biskup S, Puskás C, Berg D, Synofzik M. Atypical parkinsonism in C9orf72 expansions: a case report and systematic review of 45 cases from the literature. J Neurol. 2016;263:558–74. PubMed PMID: 26810719.

Zou ZY, Li XG, Liu MS, Cui LY. Screening for C9orf72 repeat expansions in Chinese amyotrophic lateral sclerosis patients. Neurobiol Aging. 2013;34:1710.e5–6.

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