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C9orf72-related amyotrophic lateral sclerosis and frontotemporal dementia

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## /C9orf72/-Related Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

Synonyms: c9FTD/ALS, /C9orf72/-Related ALS/FTD

Marc Cruts, PhD

Department of Molecular Genetics

VIB

Institute Born-Bunge

University of Antwerp

Antwerp, Belgium

eb.au-biv.neglom@sturC.craM <mailto:dev@null>

Sebastiaan Engelborghs, MD, PhD

Reference Center for Biological Markers of Dementia (BIODEM)

Institute Born-Bunge

University of Antwerp

Antwerp, Belgium

eb.neprewtnau@shgroblegne.naaitsabes <mailto:dev@null>

Julie van der Zee, PhD

Department of Molecular Genetics

VIB

Institute Born-Bunge

University of Antwerp

Antwerp, Belgium

eb.au-biv.neglom@eeZrednav.eiluJ <mailto:dev@null>

Christine Van Broeckhoven, PhD, DSc

Department of Molecular Genetics

VIB

Institute Born-Bunge

University of Antwerp

Antwerp, Belgium

eb.au-biv.neglom@nevohkceorBnaV.enitsirhC <mailto:dev@null>

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### Summary

#### Disease characteristics.

/C9orf72/-related amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is characterized by:

\*

Motor neuron disease, including upper or lower motor neuron dysfunction (or both) that may or may not fulfill criteria for the ALS phenotype;

\*

Frontotemporal lobar degeneration (FTLD), including progressive changes in behavior, executive dysfunction, and/or language impairment; and

\*

Some degree of parkinsonism (typically of the akinetic-rigid type without tremor that is levodopa unresponsive).

Age at onset is usually 30-70 years (range: 27 to 85 years) irrespective of the presenting symptoms. Initial manifestations may be pure FTLT or pure ALS; additional symptoms may appear during the disease course. Life expectancy is highly variable and mainly associated with the clinical manifestations.

#### Diagnosis/testing.

Brain MRI typically shows symmetric bilateral frontal (most pronounced mesial frontal) ± temporal ± parietal ± cingulate cortex atrophy. FDG PET typically shows hypometabolism predominantly in fronto/temporal areas. The diagnosis of /C9orf72/-related ALS/FTLD is established by detection of a heterozygous /C9orf72/ pathogenic GGGGCC (G<sub>4</sub>C<sub>2</sub>) hexanucleotide repeat expansion on molecular genetic testing.

#### Management.

/Treatment of manifestations:/ Motor neuron disease manifestations are treated as for ALS of other causes. Non-pharmacologic treatment options in FTLD include psychosocial support and education to reduce caregiver stress and burden as well as environmental, behavioral, and physical interventions designed to minimize the occurrence and consequences of undesired behaviors. Pharmacologic treatment should be considered when non-pharmacologic treatment options have failed or when behavioral and psychological signs and symptoms (as in FTLD) are dangerous or too stressful.

/Surveillance:/ Clinical, neurologic, and neuropsychological follow up is necessary.

#### Genetic counseling.

/C9orf72/-related ALS/FTD is inherited in an autosomal dominant manner, with age-dependent penetrance. Although most affected individuals have an affected parent, the parents may be unaffected because of either incomplete or age-dependent penetrance in the parent or /de novo/ mutation in the proband. Each child of an individual with /C9orf72/-related ALS/FTD has a 50% chance of inheriting the pathogenic /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion. Prenatal testing for pregnancies at increased risk is possible if the pathogenic /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion has been identified in an affected family member; however, requests for prenatal testing for adult-onset conditions such as /C9orf72/-related ALS/FTD are not common.

#### Diagnosis

##### Suggestive Findings

/C9orf72/-related amyotrophic lateral sclerosis (ALS) and frontotemporal

dementia (FTD) should be suspected in probands with the following [Boeve & Graff-Radford 2012 <#als-ftd.REF.boeve.2012.29>, Van Langenhove et al 2013 <#als-ftd.REF.van\_langenhove.2013.365>]:

\*

**\*Clinical findings\***

○

Frontotemporal lobar degeneration (FTLD) characterized by progressive changes in behavior, executive dysfunction, and/or language impairment. Of the three FTLD clinical syndromes, behavioral variant FTD (bvFTD) is most often, but not exclusively, present. It is characterized by progressive behavioral impairment and a decline in executive function with predominant frontal lobe atrophy on brain MRI.

○

Motor neuron disease, including upper or lower motor neuron dysfunction (or both) that may or may not fulfill criteria for the full ALS phenotype

○

Some degree of parkinsonism, which is present in many individuals with /C9orf72/-related bvFTD, is typically of the akinetic-rigid type without tremor, and is levodopa unresponsive [Boeve et al 2012 <#als-ftd.REF.boeve.2012.765>]

○

The phenotype of behavioral variant FTD (bvFTD) ± ALS ± parkinsonism in the proband and his/her relatives

○

Age at onset usually 30-70 years

\*

**\*Family history\*** of dementia and/or ALS consistent with autosomal dominant inheritance, including simplex cases (i.e., a single occurrence in a family)

\*

**\*Neuroimaging\*** showing symmetric bilateral frontal (most pronounced mesial frontal) ± temporal ± parietal ± cingulate cortex atrophy on brain MRI [Whitwell et al 2012 <#als-ftd.REF.whitwell.2012.794>]. The cerebellum and thalamus have also been noted as potential regions of atrophy in persons with /C9orf72/-related ALS/FTD [Mahoney et al 2012 <#als-ftd.REF.mahoney.2012.41>, Sha et al 2012 <#als-ftd.REF.sha.2012.1002>, Whitwell et al 2012 <#als-ftd.REF.whitwell.2012.794>].

FDG-PET predominantly shows hypometabolism in frontotemporal areas.

\*

**\*Neuropsychological examination\***

○

Implication of the frontosubcortical neural networks with executive dysfunction in association with visuospatial dysfunction and memory impairment

○

Language impairment (relatively common but rarely the predominant phenotype)

**Establishing the Diagnosis**

The diagnosis of /C9orf72/-related ALS/FTD is established by detection of a heterozygous pathogenic GGGGCC (G<sub>4</sub> C<sub>2</sub>) hexanucleotide repeat

expansion in /C9orf72/ on molecular genetic testing [Dejesus-Hernandez et al 2011 <#als-ftd.REF.dejesushernandez.2011.245>, Renton et al 2011 <#als-ftd.REF.renton.2011.257>, Gijssels et al 2012 <#als-ftd.REF.gijssels.2012.54>].

Note: As /C9orf72/ G<sub>4</sub>C<sub>2</sub> repeat expansions are to date the most frequent cause of ALS and FTD in simplex cases (i.e., a single occurrence in a family) [Cruts et al 2013 <#als-ftd.REF.cruts.2013.450>], /C9orf72/ molecular genetic testing should include simplex cases as well as those with a positive familial history. 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.

### Allele Sizes

The size of the G<sub>4</sub>C<sub>2</sub> hexanucleotide repeats in /C9orf72/ alleles ranges from two repeats to more than 4000 repeats [Buchman et al 2013 <#als-ftd.REF.buchman.2013.12>, van Blitterswijk et al 2013 <#als-ftd.REF.van\_blitterswijk.2013.978>]. The pathogenic nature of the repeat depends on its size; however, a precise cut-off between normal and pathogenic alleles is complicated by multiple factors.

\*Normal alleles.\* Repeat sizes <25 G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat units are generally considered normal [Majounie et al 2012c <#als-ftd.REF.majounie.2012c.323>, van der Zee et al 2013 <#als-ftd.REF.van\_der\_zee.2013.363>] (see Note).

\*Pathogenic high penetrance alleles.\* In most reports, repeat sizes >60 G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat units are considered pathogenic (see Note).

Note: The minimal size of a G<sub>4</sub>C<sub>2</sub> pathogenic repeat is under debate: some studies consider repeats of >30 G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat units as pathogenic, whereas others use a cut-off of 60 G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat units. Setting a sharp size cut-off between normal and pathogenic repeats is complicated by the following:

\*

A recent study that found an expansion of 50 G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat units with supportive evidence of cosegregation with disease in a family with ALS/FTD [I Gijssels, personal communication]

\*

The rare occurrence of G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat sizes between 25 and 60 repeat units in the general population. Rare alleles of 25-50 repeat units were observed in FTLD, ALS, and related disorders; however, cosegregation with disease was not observed in families, and older healthy individuals heterozygous for alleles in the same size range have been reported [Xi et al 2012 <#als-ftd.REF.xi.2012.1583>].

\*

Variability in the methods and their precision in detecting larger repeats (~>80) of G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat units:

o

Southern blot hybridization analysis, preferably after size separation of fragmented genomic DNA by pulsed-field gel electrophoresis, is optimal [Akimoto et al 2014 <#als-ftd.REF.akimoto.2014.419>]. However, it requires

biomaterials, expertise and equipment that are not commonly available in clinical laboratories.

- Widespread use of G<sub>4</sub>C<sub>2</sub>-repeat-primed PCR which identifies alleles >60 G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat units but cannot determine the number of repeat units
- Instability of large G<sub>4</sub>C<sub>2</sub> hexanucleotide repeats, which may result in somatic mosaicism, as observed by smeared instead of discrete bands on Southern blots [I Gijselinck, personal communication]

In most settings, a pathogenic G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion is detected using a repeat-primed PCR assay (RP-PCR), ideally accompanied with a PCR amplicon fragment length assay.

- \* RP-PCR allows the detection of an expanded repeat allele as an allele being larger than about 60 G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat units in size, without further indication of the exact repeat length.
- \* PCR amplicon fragment length assay provides the exact repeat length of alleles with up to about 80 G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat units [van der Zee et al 2013 <#als-ftd.REF.van\_der\_zee.2013.363>; Akimoto et al 2014 <#als-ftd.REF.akimoto.2014.419>; I Gijselinck, personal communication].

Table 1.

Summary of Molecular Genetic Testing Used in /C9orf72/-Related Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

View in own window

</books/NBK268647/table/als-ftd.T.summary\_of\_molecular\_genetic\_t/?report=objectonly>

Gene ^1	Test Method	Variants Detected	Proportion of Probands with
a	Pathogenic Variant Detectable by This Method		
/C9orf72/	Targeted mutation analysis ^2	Number of G <sub>4</sub> C <sub>2</sub>	
hexanucleotide repeat units ^3, 4		74%-100% ^5	

1.

See Table A. Genes and Databases </books/NBK268647/#als-ftd.molgen.TA> for chromosome locus and protein name. See Molecular Genetics <#als-ftd.Molecular\_Genetics> for information on allelic variants.

2.

Refers to combined testing of RP-PCR and fragment length analysis; Southern blotting was proposed as the gold standard in a clinical diagnostic setting [Akimoto et al 2014 <#als-ftd.REF.akimoto.2014.419>].

3.

G\_4 C\_2 = GGGGCC

4.

This is the only proven pathogenic mutation in /C9orf72/ reported to date.

5.

Akimoto et al [2014] <#als-ftd.REF.akimoto.2014.419>

### Genetically Related (Allelic) Disorders

While pathogenic /C9orf72/ G\_4 C\_2 hexanucleotide repeat expansions are likely associated with causation of diseases of the ALS/FTD complex only, contribution to the genetic risk profile of other neurodegenerative diseases cannot be excluded [Cruts et al 2013 <#als-ftd.REF.cruts.2013.450>].

In extended series of individuals with clinically diagnosed Alzheimer disease </books/n/gene/alzheimer/> (AD), a /C9orf72/ pathogenic G\_4 C\_2 hexanucleotide repeat expansion was observed in fewer than 1%, a frequency comparable to that found in neurologically healthy individuals. When available, neuropathologic findings were consistent with a definite diagnosis of FTLN with or without limited secondary AD-like pathology [Murray et al 2011 <#als-ftd.REF.murray.2011.673>, Majounie et al 2012b <#als-ftd.REF.majounie.2012b.283>]. Similar observations were made in individuals with Parkinson disease </books/n/gene/parkinson-overview/> (PD) [Majounie et al 2012a <#als-ftd.REF.majounie.2012a.2527.e1>, Theuns et al 2014 <#als-ftd.REF.theuns.2014.1906>]. Together these findings suggest that the association of /C9orf72/ G\_4 C\_2 hexanucleotide repeat expansions with AD and PD is the result of relatively common AD or PD pathology occurring as a secondary phenomenon in an individual with primary /C9orf72/-related disease.

A /C9orf72/ G\_4 C\_2 hexanucleotide repeat expansion was observed in 6.5% of individuals with a diagnosis of depressive pseudodementia [Bieniek et al 2014 <#als-ftd.REF.bieniek.2014.775>] and in 2% of Huntington disease </books/n/gene/huntington/> phenocopies lacking a /HTT/ CAG trinucleotide repeat expansion [Beck et al 2013 <#als-ftd.REF.beck.2013.345>, Hensman Moss et al 2014 <#als-ftd.REF.hensman\_moss.2014.292>].

### Clinical Description

#### Natural History

Individuals with a pathogenic /C9orf72/ G\_4 C\_2 hexanucleotide repeat expansion are diagnosed with diseases of the frontotemporal lobar degeneration (FTLD) / amyotrophic lateral sclerosis (ALS) complex. Of note, juvenile ALS has not been associated with such /C9orf72/ G\_4 C\_2 hexanucleotide repeat expansions [Stewart et al 2012 <#als-ftd.REF.stewart.2012.409>].

If and at what age symptoms will become apparent is unpredictable and variable even among members of the same family who are heterozygous for a /C9orf72/ G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion [Boeve et al 2012 <#als-ftd.REF.boeve.2012.765>].

Occasionally, individuals heterozygous for a pathogenic G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion greater than 60 repeat units remain free of clinical symptoms, even in old age [Van Langenhove et al 2013 <#als-ftd.REF.van\_langenhove.2013.365>]. See Penetrance <#als-ftd.Penetrance>.

Age of onset is highly variable (range: 27-85 years) irrespective of the presenting symptoms [Cruts et al 2013 <#als-ftd.REF.cruts.2013.450>]. The mean is about 58.0 ± 8 years [Majounie et al 2012c <#als-ftd.REF.majounie.2012c.323>, van der Zee et al 2013 <#als-ftd.REF.van\_der\_zee.2013.363>].

Initially the manifestations may be pure FTLD or ALS; additional symptoms may appear during the disease course.

\*FTLD.\* The three FTLD clinical syndromes are behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent/agrammatic aphasia variant PPA (nfvPPA). Most (not all) individuals with /C9orf72/-related FTLD present with bvFTD [Cooper-Knock et al 2014 <#als-ftd.REF.cooperknock.2014.333>].

/C9orf72/-related bvFTD includes the full spectrum of bvFTD behavioral changes: early disinhibition, early apathy or inertia, early loss of empathy, hyperorality, and dietary changes. Disinhibition is the most prominent behavioral feature [Van Langenhove et al 2013 <#als-ftd.REF.van\_langenhove.2013.365>]. /C9orf72/-related bvFTD is associated with psychosis [Devenney et al 2014 <#als-ftd.REF.devenney.2014.331>]. Brain MRI shows predominant frontal lobe atrophy.

Some individuals with C9orf72 FTD have a choreiform movement disorder which (especially when combined with behavioral abnormalities) may be confused with Huntington disease </books/n/gene/huntington/> [Hensman Moss et al 2014 <#als-ftd.REF.hensman\_moss.2014.292>].

Age of onset of /C9orf72/-related FTLD was later than in FTLD caused by mutation of /MAPT/ (see /MAPT/-Related Disorders </books/n/gene/ftdp-17/>) and was similar to /GRN/-related FTLD </books/n/gene/ftd-grn/> and genetically unresolved FTLD [Van Langenhove et al 2013 <#als-ftd.REF.van\_langenhove.2013.365>].

\*ALS.\* The entire clinical spectrum of ALS (which includes abnormal muscle tone and tendon reflexes, fasciculations, muscle cramps, and gait disturbances) occurs in /C9orf72/-related ALS. /C9orf72/-related ALS is associated with spinal symptoms (involving limb muscles) in 60%-70% of affected individuals and bulbar symptoms (including swallowing and speech) in 30%-40% [Majounie et al 2012c <#als-ftd.REF.majounie.2012c.323>, Cruts et al 2013 <#als-ftd.REF.cruts.2013.450>]. Bulbar onset has been associated with /C9orf72/-related ALS [Cooper-Knock et al 2014 <#als-ftd.REF.cooperknock.2014.333>].

Compared to the range of the age of onset in hereditary ALS  
</books/n/gene/als-overview/> of other causes, the age of onset of  
/C9orf72/-related ALS is similar to that in persons with ALS1 (caused by  
mutation of /SOD1/), but older than in persons with ALS6 (caused by  
mutation of /FUS)/.

\*Life expectancy\* is highly variable and mainly associated with the  
clinical diagnosis.

\*

For ALS, /C9orf72/ G\_4 C\_2 hexanucleotide repeat expansions were  
associated with disease duration ranging from three to 96 months,  
comparable to ALS6 (mutation of /FUS/), and at the lower end of the  
range associated with ALS1 (mutation of /SOD1/) and /TARDBP/-related  
ALS </books/n/gene/tardbp-als/> or genetically unspecified ALS.

\*

For FTLT, disease duration ranged from one to 22 years, similar to  
that observed in other genetic types of FTLT. As expected, survival  
in FTLT was markedly compromised (on average 1.8 years) when ALS  
symptoms became apparent [Van Langenhove et al 2013  
<#als-ftd.REF.van\_langenhove.2013.365>].

### Genotype-Phenotype Correlations

Clinical findings cannot predict the presence of an expanded /C9orf72/  
G\_4 C\_2 hexanucleotide repeat allele nor can the presence of an expanded  
G\_4 C\_2 hexanucleotide repeat allele predict the disease course in any  
given individual.

### Penetrance

Penetrance related to /C9orf72/ G\_4 C\_2 repeat size has not yet been  
fully studied.

Heterozygosity for a pathogenic /C9orf72/ G\_4 C\_2 hexanucleotide repeat  
expansion is associated with age-dependent cumulative disease penetrance  
estimated as follows [Majounie et al 2012c  
<#als-ftd.REF.majounie.2012c.323>, Benussi et al 2014  
<#als-ftd.REF.benussi.2014.799>]:

\*

~0% at age 35 years

\*

50% at age 58 years

\*

Nearly 100% at age 80 years

Reduced penetrance was also supported by the presence of elderly,  
neurologically healthy obligate G\_4 C\_2 hexanucleotide repeat expansion  
heterozygotes in families with frontotemporal lobar degeneration-motor  
neuron disease (FTLT-MND) and the observation of G\_4 C\_2 hexanucleotide  
repeat expansions in 0.2%-0.6% of unaffected community controls,  
including the elderly [Cruts et al 2013 <#als-ftd.REF.cruts.2013.450>].

### Anticipation

Direct evidence of genetic anticipation resulting from an intergenerational increase in the number of G<sub>4</sub>C<sub>2</sub> hexanucleotide repeats has not been demonstrated; however, a seven- to ten-year decrease in age of onset in the younger of two consecutive generations of families with ALS/FTD segregating a /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion has been reported [Boeve et al 2012 <#als-ftd.REF.boeve.2012.765>, Chiò et al 2012 <#als-ftd.REF.chi\_.2012.784>, Benussi et al 2014 <#als-ftd.REF.benussi.2014.799>].

## Prevalence

Detailed epidemiologic studies of the prevalence of the /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion have not been performed. Rough estimates based on the estimated prevalence of the clinical syndromes and /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion frequencies in patient cohorts result in the following:

\*

\*ALS.\* The prevalence of ALS is estimated at 4-8:100,000 [Traynor et al 1999 <#als-ftd.REF.traynor.1999.504>]. With an average /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion frequency in ALS patient cohorts of 10% [Majounie et al 2012c <#als-ftd.REF.majounie.2012c.323>], a rough estimate of /C9orf72/-related ALS is in the order of 0.4-0.8 per 100,000.

\*

\*FTLD.\* Detailed epidemiologic studies of FTLD have not been described. One UK study estimated the prevalence of FTLD at 15:100,000 in the 45- to 64-year-old population [Ratnavalli et al 2002 <#als-ftd.REF.ratnavalli.2002.1615>]. With an average /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion frequency of 10% in FTLD cohorts [Majounie et al 2012c <#als-ftd.REF.majounie.2012c.323>, van der Zee et al 2013 <#als-ftd.REF.van\_der\_zee.2013.363>], a rough estimate of /C9orf72/-related FTLD is in the order of 1.5:100,000.

/C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansions were observed at frequencies of up to 29%, 50%, and 88% in frontotemporal lobar degeneration (FTLD), amyotrophic lateral sclerosis (ALS), and ALS/FTD research cohorts, respectively [Cruts et al 2013 <#als-ftd.REF.cruts.2013.450>].

The frequency of pathogenic /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansions was about twice as high in individuals with a family history of FTLD and/or ALS compared to those without a family history of these disorders. Of note, because only 10% of individuals with ALS have a positive family history, simplex cases (i.e., a single occurrence in a family) outnumbered familial cases among individuals with ALS resulting from an expanded /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat allele.

The frequency of /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansions significantly exceeds that of mutations in any other FTLD- or ALS-related gene. The highest mutation frequencies were recorded in individuals with symptoms of both FTLD and ALS, and a positive family history of these disorders. In this group of individuals with ALS/FTD, /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansions are the only known common mutation.

It is important to note that /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion frequencies greatly depend on ethnicity and geographic region. The highest repeat expansion frequencies were observed in patient cohorts of northern European heritage. Markedly elevated frequencies were reported in Scandinavian countries [Majounie et al 2012c <#als-ftd.REF.majounie.2012c.323>, Lindquist et al 2013 <#als-ftd.REF.lindquist.2013.279>, Smith et al 2013 <#als-ftd.REF.smith.2013.102>, van der Zee et al 2013 <#als-ftd.REF.van\_der\_zee.2013.363>]. By contrast, individuals of Asian heritage with /C9orf72/ G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansions were rare [Majounie et al 2012c <#als-ftd.REF.majounie.2012c.323>, Tsai et al 2012 <#als-ftd.REF.tsai.2012.2232.e11>, Jang et al 2013 <#als-ftd.REF.jang.2013.1311>, Konno et al 2013 <#als-ftd.REF.konno.2013.398>, Zou et al 2013 <#als-ftd.REF.zou.2013.1710>].

### Differential Diagnosis

Differential diagnosis for /C9orf72/-related frontotemporal lobar degeneration (FTLD):

- \* Dementia, especially with abnormal behavior. Differential diagnosis includes Alzheimer disease (see Alzheimer Disease Overview </books/n/gene/alzheimer/> and Early-Onset Familial Alzheimer Disease </books/n/gene/alzheimer-early/>), diffuse Lewy Body disease, Huntington disease </books/n/gene/huntington/>, other forms of frontotemporal dementia (FTD) (see /GRN/-Related Frontotemporal Dementia </books/n/gene/ftd-grn/>, and /MAPT/-Related Disorders </books/n/gene/ftdp-17/>), prion disease </books/n/gene/prion/>, and even schizophrenia or bipolar disease.
- \* Autosomal dominant or sporadic Alzheimer disease with a specific clinical presentation (and/or early onset) (see Alzheimer Disease Overview </books/n/gene/alzheimer/> and Early-Onset Familial Alzheimer Disease </books/n/gene/alzheimer-early/>). The use of Alzheimer disease biomarkers helps differentiate between Alzheimer disease and FTLD [Dubois et al 2014 <#als-ftd.REF.dubois.2014.614>].

Differential diagnosis for /C9orf72/-related amyotrophic lateral sclerosis (ALS):

- \* Compressive (cervical) myelopathy, which can mimic upper motor signs
- \* Chronic inflammatory polyradiculoneuropathy as well as multifocal motor, toxic, or metabolic neuropathies or myopathies such as inclusion body myositis </books/n/gene/ibmpfd/> or polymyositis, all of which can mimic lower motor signs
- \* Other forms of upper and/or lower motor neuron diseases (see Amyotrophic Lateral Sclerosis Overview </books/n/gene/als-overview/>) and various forms of spinal muscular atrophy </books/n/gene/sma/>
- \* A rare ALS variant of prion disease </books/n/gene/prion/> [Worrall

et al 2000 <#als-ftd.REF.worrall.2000.33>]

\*Note to clinicians:\* For a patient-specific 'simultaneous consult' related to this disorder, go to SimulConsult<sup>®</sup> <[http://www.simulconsult.com/run/?u=elthat\\_130617045940&t=d](http://www.simulconsult.com/run/?u=elthat_130617045940&t=d)>, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with /C9orf72/-related amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD), the following evaluations are recommended:

- \* General medical history with emphasis on psychiatric illness [Devenney et al 2014 <#als-ftd.REF.devenney.2014.331>] and problems potentially related to FTD such as alcohol or drug abuse
- \* Family history with attention to dementia, ALS, or psychiatric illness, which are present in many /C9orf72/ heterozygotes [Devenney et al 2014 <#als-ftd.REF.devenney.2014.331>]
- \* Physical and clinical neurologic examination with attention to physical disability related to motor neuron disease
- \* Neuropsychological examination to evaluate the extent and profile of cognitive disturbance
- \* Electromyography in case of ALS and/or lower motor signs
- \* Assessment of need for ancillary equipment such as walker, wheelchair, and/or respiratory assistance
- \* Discussion of advanced care planning

### Treatment of Manifestations

For ALS-related treatment options refer to Amyotrophic Lateral Sclerosis Overview </books/n/gene/als-overview/>.

\*Psychosocial support and education\* are indicated to reduce caregiver stress and reduce the risk of caregiver burden.

\*Non-pharmacologic treatment options\* in frontotemporal lobar degeneration (FTLD) include psychosocial support and education as well as environmental, behavioral, and physical interventions designed to minimize the occurrence and consequences of undesired behaviors. Caregiver and patient support groups are valuable.

Additional helpful interventions include physical, occupational and speech therapy, home safety evaluations, and the implementation of

augmentative communication devices [Rabinovici & Miller 2010 <#als-ftd.REF.rabinovici.2010.375>].

Physical, occupational, and speech therapy are very valuable in cases involving parkinsonism and/or lower/upper motor neuron signs.

\*Pharmacologic treatment\* should be considered when non-pharmacologic treatment options have failed or when behavioral and psychological signs and symptoms (as in FTLD) are dangerous or too stressful. Options include:

\*

SSRIs. Although the reported efficacy of SSRIs in treating FTLD is based on relatively small, often uncontrolled trials, the use of SSRIs is considered first line therapy in FTLD with behavioral and psychological signs and symptoms [Rabinovici & Miller 2010 <#als-ftd.REF.rabinovici.2010.375>].

\*

Venlafaxine. When apathy is prominent, venlafaxine may be tried for its activating properties.

\*

Bupropion is considered when parkinsonism is present because of its dopaminergic tone [Rabinovici & Miller 2010 <#als-ftd.REF.rabinovici.2010.375>].

\*

Atypical antipsychotics may be considered in patients with severe behavioral and psychological signs and symptoms (agitation, aggressiveness, psychosis) that are refractory to SSRIs. Often, atypical antipsychotics are necessary only as a temporizing measure, and can be tapered as patients become more apathetic (and thus less agitated and disinhibited) with disease progression [Rabinovici & Miller 2010 <#als-ftd.REF.rabinovici.2010.375>].

## Surveillance

Clinical, neurologic, and neuropsychological follow up is necessary.

## Evaluation of Relatives at Risk

See Genetic Counseling <#als-ftd.Related\_Genetic\_Counseling\_Issue> for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Search ClinicalTrials.gov <<http://clinicaltrials.gov/>> for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder

## Genetic Counseling

/Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional/. -ED.

#### Mode of Inheritance

/C9orf72/-related amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD) is inherited in an autosomal dominant manner, with age-dependent penetrance.

#### Risk to Family Members

##### \*Parents of a proband\*

\*

Most individuals with /C9orf72/-related ALS/FTD have an affected parent.

\*

The parents of an individual diagnosed with /C9orf72/-related ALS/FTD may be unaffected for one of the following reasons:

o

Incomplete or age-dependent penetrance in the parent (i.e., the parent may be too young to manifest the disorder). See Penetrance <#als-ftd.Penetrance>.

OR

o

/De novo/ mutation in the proband

+

Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine the /de novo/ mutation rate, the proportion of /C9orf72/-related ALS/FTD caused by /de novo/ mutation is unknown, but presumed to be low.

+

A proven /de novo/ repeat expansion has been reported only once [I Gijssels, personal communication].

\*

Molecular genetic testing of parents may determine that one is heterozygous for the /C9orf72/ G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: Although most individuals diagnosed with /C9orf72/-related ALS/FTD have an affected parent, the family history 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.

##### \*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 has the /C9orf72/ G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion, the risk to the sibs of inheriting the expansion is 50%.

\*

The sibs of a proband with clinically unaffected parents are still at increased risk for /C9orf72/-related ALS/FTD because one of the parents may have:

o

Age-dependent penetrance <#als-ftd.Penetrance>;

OR

o

Germline mosaicism of the expanded repeat.

\*Offspring of a proband.\* Each child of an individual with /C9orf72/-related ALS/FTD has a 50% chance of inheriting the pathogenic /C9orf72/ G<sub>4</sub> C<sub>2</sub> hexanucleotide 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<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion, his or her family members may be at risk.

#### Related Genetic Counseling Issues

\*Considerations in families with an apparent /de novo/ mutation.\* When neither parent of a proband with /C9orf72/-related ALS/FTD has the /C9orf72/ G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion or clinical evidence of the disorder, the /C9orf72/ G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion is likely /de novo/. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

\*Testing of at-risk asymptomatic adults relatives\* of individuals with /C9orf72/-related ALS/FTD is possible after molecular genetic testing <<http://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/molecular-genetic-testing/>>

has identified the /C9orf72/ G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion in the family. Such testing should be performed in the context of formal genetic counseling <<http://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/genetic-counseling/>>.

This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. Testing of asymptomatic at-risk individuals with nonspecific or equivocal symptoms is predictive testing

<<http://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/predictive-testing/>>,

not diagnostic testing

<<http://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/diagnostic-testing/>>.

Testing for the pathogenic /C9orf72/ G\_4 C\_2 hexanucleotide repeat expansion in the absence of definite symptoms of the disease is predictive testing. At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply "the need to know."

\*Testing of asymptomatic individuals younger than age 18 years\* who are at risk for adult-onset disorders for which no treatment exists is not considered appropriate, 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.

Testing is appropriate to consider in symptomatic individuals (regardless of age) in a family with an established diagnosis of /C9orf72/-related ALS/FTD.

For more information, see also the National Society of Genetic Counselors position statement <http://nsgc.org/p/bl/et/blogid=47&blogaid=28> on genetic testing of minors for adult-onset conditions and the American Society of Human Genetics and American College of Medical Genetics points to consider <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1801355/pdf/ajhg00037-0249.pdf>: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.

\*Family planning\*

\*

The optimal time for determination of genetic risk and discussion of the availability of prenatal 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.

\*DNA banking\* is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

### Prenatal Testing

If the pathogenic /C9orf72/ G\_4 C\_2 hexanucleotide repeat expansion has been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing for this disease/gene or custom prenatal testing.

Requests for prenatal testing for adult-onset conditions such as /C9orf72/-related ALS/FTD are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for

the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

\*Preimplantation genetic diagnosis (PGD)\* may be an option for some families in which the pathogenic /C9orf72/ G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion has been identified.

## 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 </books/n/gene/app4/>./

\*

\*Amyotrophic Lateral Sclerosis Association (ALS Association)\*  
27001 Agoura Road  
Suite 250  
Calabasas Hills CA 91301-5104  
\*Phone:\* 800-782-4747 (Toll-free Patient Services); 818-880-9007  
\*Fax:\* 818-880-9006  
\*Email:\* alsinfo@alsa-national.org  
www.alsa.org <<http://www.alsa.org>>

\*

\*Amyotrophic Lateral Sclerosis Society of Canada\*  
3000 Steeles Avenue East  
Suite 200  
Markham Ontario L3R 4T9  
Canada  
\*Phone:\* 800-267-4257 (toll-free); 905-248-2052  
\*Fax:\* 905-248-2019  
www.als.ca <<http://www.als.ca>>

\*

\*Association for Frontotemporal Degeneration (AFTD)\*  
290 King of Prussia Road  
Radnor Station Building #2, Suite 320  
Radnor PA 19087  
\*Phone:\* 866-507-7222 (Toll-free Helpline); 267-514-7221  
\*Email:\* info@theaftd.org  
www.theaftd.org <<http://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](mailto:info@lesturnerals.org)  
<http://www.lesturnerals.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 Frontotemporal Dementia: Genes and Databases

View in own window

[</books/NBK268647/table/als-ftd.molgen.TA/?report=objectonly>](#)

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
/C9orf72/	<a href="#">&lt;/gene/203228&gt;</a>	9p21.2		
	<a href="http://www.ncbi.nlm.nih.gov/projects/mapview/maps.cgi?taxid=9606&amp;chr=9&amp;query=C9orf72&amp;qstr=C9orf72&amp;maps=snp,genes-r,pheno&amp;zoom=2">http://www.ncbi.nlm.nih.gov/projects/mapview/maps.cgi?taxid=9606&amp;chr=9&amp;query=C9orf72&amp;qstr=C9orf72&amp;maps=snp,genes-r,pheno&amp;zoom=2</a>			
	Uncharacterized protein C9orf72 <a href="http://www.uniprot.org/uniprot/Q96LT7">http://www.uniprot.org/uniprot/Q96LT7</a>			
	alsod/C9orf72 genetic mutations			
	<a href="http://alsod.iop.kcl.ac.uk/Als/Overview/gene.aspx?gene_id=C9orf72">http://alsod.iop.kcl.ac.uk/Als/Overview/gene.aspx?gene_id=C9orf72</a>			
	Alzheimer Disease & Frontotemporal Dementia Mutation Database (C9orf72)			
	<a href="http://www.molgen.vib-ua.be/ADMutations/Default.cfm?MT=1&amp;ML=1&amp;Page=MutByQuery&amp;Query=tblContexts.ID=11&amp;Selection=Gene%20=%20C9orf72">http://www.molgen.vib-ua.be/ADMutations/Default.cfm?MT=1&amp;ML=1&amp;Page=MutByQuery&amp;Query=tblContexts.ID=11&amp;Selection=Gene%20=%20C9orf72</a>			
	C9orf72 <a href="http://www.hgmd.cf.ac.uk/ac/gene.php?gene=C9orf72%20">http://www.hgmd.cf.ac.uk/ac/gene.php?gene=C9orf72%20</a>			

Data are compiled from the following standard references: gene symbol from HGNC <http://www.genenames.org/index.html>; chromosomal locus, locus name, critical region, complementation group from OMIM <http://www.omim.org/>; protein name from UniProt <http://www.uniprot.org/>. For a description of databases (Locus Specific, HGMD) to which links are provided, click [here](#)

[</books/n/gene/appl/>](#).

Table B. OMIM Entries for C9orf72-Related Amyotrophic Lateral Sclerosis and Frontotemporal Dementia (View All in OMIM [</omim/105550,614260>](#))

View in own window

[</books/NBK268647/table/als-ftd.molgen.TB/?report=objectonly>](#)

105550	<a href="#">&lt;/omim/105550&gt;</a>	FRONTOTEMPORAL DEMENTIA AND/OR AMYOTROPHIC LATERAL SCLEROSIS 1; FTDALS1
614260	<a href="#">&lt;/omim/614260&gt;</a>	CHROMOSOME 9 OPEN READING FRAME 72; C9ORF72

## Molecular Genetic Pathogenesis

The molecular basis of /C9orf72/-related ALS/FTD is not fully understood. At least some evidence of the involvement of diverse disease mechanisms associated with repeat expansion diseases is reported [Cruts et al 2013 [<#als-ftd.REF.cruts.2013.450>](#)]:

\*

RNA toxicity caused by sequestration of RNA-binding proteins (RBPs)

and normal /C9orf72/ transcripts by RNA species containing the pathogenic G<sub>4</sub> C<sub>2</sub> (GGGGCC) hexanucleotide repeat expansion into nuclear foci, thereby interfering with their physiologic functions [Mori et al 2013b <#als-ftd.REF.mori.2013b.413>]

\*

Haploinsufficiency due to loss of expression of /C9orf72/ from the G<sub>4</sub> C<sub>2</sub> expanded allele [van der Zee et al /2/013; I Gijselinck, personal communication]

\*

G<sub>4</sub> C<sub>2</sub> repeat-associated, non-ATG initiated bidirectional translation of illicitly transcribed expanded G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat sequences into diverse aggregation-prone dipeptide repeat proteins [Mori et al 2013a <#als-ftd.REF.mori.2013a.881>, Mori et al 2013c <#als-ftd.REF.mori.2013c.1335>]

**\*Gene structure.\*** /C9orf72/ comprises 12 exons. It is transcribed into three major transcript variants encoding two different protein isoforms. Among other differences, the transcript variants use alternative first exons. Relative to these transcript variants, the G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat that is expanded in /C9orf72/-related ALS/FTD is located either upstream or in the first intron following the first non-coding exon [Cruts et al 2013 <#als-ftd.REF.cruts.2013.450>]. For a detailed summary of gene and protein information, see Table A </books/NBK268647/#als-ftd.molgen.TA>, **\*Gene Symbol\*.**

**\*Benign allelic variants.\*** The G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion is typically considered benign if the number of repeat units is lower than 25. See Diagnosis, Allele Sizes <#als-ftd.Allele\_Sizes> for details of benign (normal) and pathogenic variants.

**\*Pathogenic allelic variants.\*** The G<sub>4</sub> C<sub>2</sub> hexanucleotide repeat expansion is the only known pathogenic variant in /C9orf72/-related ALS/FTD. There is currently no evidence that variants that alter the C9orf72 protein sequence are pathogenic.

See Diagnosis, Allele Sizes <#als-ftd.Allele\_Sizes> for details of normal and pathogenic variants.

Table 2.

/C9orf72/ Variants Discussed in This /GeneReview/

View in own window

</books/NBK268647/table/als-ftd.T.c9orf72\_variants\_discussed\_in/?report=objectonly>

Variant Classification DNA Nucleotide Change Protein Amino Acid Change Reference Sequences

**\*Benign\*** g.5321GGGGCC(2\_25) 1 NA NG\_031977.1  
<[http://www.ncbi.nlm.nih.gov/nuccore/NG\\_031977.1](http://www.ncbi.nlm.nih.gov/nuccore/NG_031977.1)>

**\*Pathogenic\*** g.5321GGGGCC(60\_?) 1 NA

Note on variant classification: Variants listed in the table have been provided by the authors. /GeneReviews/ staff have not independently verified the classification of variants.

Note on nomenclature: /GeneReviews/ follows the standard naming conventions of the Human Genome Variation Society ([www.hgvs.org](http://www.hgvs.org))

<<http://www.hgvs.org>>). See Quick Reference </books/n/gene/app3/> for an explanation of nomenclature.

NA, not applicable

1. See Diagnosis, Allele Sizes <#als-ftd.Alele\_Sizes>. Designation for normal range of alleles from 2-25 repeats and for pathogenic allele range of >60-?, where ? defines uncertainty.

\*Normal gene product.\* /C9orf72/ is expressed as three major transcript variants 1 to 3, encoding two protein isoforms (C9orf72a and b). The amino acid sequence of the shorter isoform C9orf72b of 222 residues is identical to the N-terminal end of the longer C9orf72a isoform of 481 residues except for the single most C-terminal amino acid. C9orf72 has no known protein domains, and its function is unknown. Based on protein sequence homology, C9orf72 is distantly related to DENN domain proteins, which are GDP/GTP exchange factors that activate Rab-GTPases [Zhang et al 2012 <#als-ftd.REF.zhang.2012.283>, Levine et al 2013 <#als-ftd.REF.levine.2013.499>] and may regulate endosomal trafficking [Farg et al 2014 <#als-ftd.REF.farg.2014.3579>].

\*Abnormal gene product.\* A pathogenic G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion does not alter the C9orf72 protein. The level of transcripts expressed from an allele containing a pathogenic G<sub>4</sub>C<sub>2</sub> hexanucleotide repeat expansion is reduced, which among other mechanisms, may contribute to disease pathogenesis (see Molecular Genetic Pathogenesis <#als-ftd.Molecular\_Genetic\_Pathogenesis>).

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## Chapter Notes

### Author Notes

The Neurodegenerative Brain Diseases group investigates the molecular mechanisms leading towards neurodegenerative dementias and related disorders. We identify novel key proteins in neurodegeneration as potential targets for early diagnosis, risk prediction, drug and biomarker development. Concurrently, we study the post-genomic consequences of disease-related genetic defects to enhance our knowledge on 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 and Parkinson disease.

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