MAYO CLINIC LABORATORIES

Test Definition: C9ORF

C9orf72 Hexanucleotide Repeat, Molecular Analysis, Varies

Overview

Useful For

Molecular confirmation of clinically suspected cases of c9FTD/ALS, frontotemporal dementia (FTD), or amyotrophic lateral sclerosis (ALS)

Presymptomatic testing for individuals with a family history of c9FTD/ALS and a documented expansion in the *C9orf72* gene

Testing Algorithm

For more information see Inherited Motor Neuron Disease and Dementia Testing Algorithm

Special Instructions

- Informed Consent for Genetic Testing
- Molecular Genetics: Neurology Patient Information
- Inherited Motor Neuron Disease Testing and Dementia Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR)

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.
Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Molecular Genetics: Neurology Patient Information
3. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting the upper and lower motor neurons. The disease is characterized by progressive spasticity, muscle wasting and paralysis, typically leading to death from respiratory failure.

Frontotemporal dementia (FTD) is a dementia syndrome that predominantly involves the frontal and temporal lobes of the brain. Clinical presentation is variable and includes progressive changes in behavior and personality and language disturbances. Affected individuals may also exhibit extrapyramidal signs.

ALS and FTD are now thought to represent an overlapping spectrum of disease. Recent literature has found that approximately 40% of familial ALS, 25% of familial FTD, and 90% of familial ALS/FTD cases have a large hexanucleotide repeat (GGGGCC) expansion in a noncoding region of *C9orf72*. At lower frequency, *C9orf72* hexanucleotide repeat expansions have also been observed in individuals with sporadic ALS, FTD, and ALS/FTD. The vast majority of individuals affected with a *C9orf72*-related disorder (c9ALS, c9FTD, or c9ALS/FTD) have hexanucleotide repeat expansions in the hundreds to thousands, while unaffected individuals have repeat sizes less than 20. The significance of repeat sizes between 20 and 100 repeats is currently unclear as both healthy controls and individuals with ALS and/or FTD

phenotypes have been reported with repeat sizes in this range.

Reference Values

Normal alleles (reference):<20 GGGGCC repeats
Indeterminate alleles: 20-100 GGGGCC repeats
Pathogenic alleles: >100* GGGGCC repeats

*The exact cutoff for pathogenicity is currently undefined. Although additional studies are needed to confirm if 100 repeats is the cutoff for pathogenicity, most individuals affected with a *C9orf72*-related disorder have C9orf72 hexanucleotide repeat expansions with hundreds to thousands of repeats.

An interpretive report will be provided.

Interpretation

An interpretive report will be provided.

Cautions

For predictive testing, it is important to first document the presence of the hexanucleotide repeat expansion in the *C9orf72* gene in an affected family member to confirm that the repeat expansion is the underlying mechanism of disease in the family.

It is strongly recommended that patients undergoing predictive testing receive genetic counseling both prior to testing and after results are available.

Predictive testing of an asymptomatic child is not recommended.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Due to somatic mosaicism, repeat size identified in the peripheral blood specimen may not reflect the repeat size in untested tissues (eg, central nervous system). In addition, a negative result does not rule out the presence of a mutation in the mosaic state that may be present but below the limit of detection of this assay (approximately 5%).

Rare sequence variants immediately downstream of the *C9orf72* repeat region may interfere with genotype results but are not expected to affect repeat-primed peaks.

Rare undocumented variants (ie, polymorphisms) in the polymerase chain reaction primer binding regions may lead to false negative results.

This test does not assess methylation status of the *C9orf72* gene.

Clinical Reference

1. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al: Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011 Oct 20;72(2):245-256
2. Renton AE, Majounie E, Waite A, et al: A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome

9p21-linked ALS-FTD. Neuron. 2011 Oct 20;72(2):257-268
3. Gijselinck I, Van Langenhove T, van der Zee J, et al: 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 Neuron. 2012 Jan;11(1):54-65
4. Majounie E, Renton AE, Mok K, et al: Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012 Apr;11(4):323-330
5. Boeve BF, Boylan KB, Graff-Radford NR, et al: Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. Brain. 2012 Mar;135(Pt 3):765-783
6. van Blitterswijk M, DeJesus-Hernandez M, Niemantsverdriet E, et al: 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 Oct;12(10):978-988
7. Nordin A, Akimoto C, Wuolikainen A, et al: 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 Jun 1;24(11):3133-3142
8. Xi Z, van Blitterswijk M, Zhang M, et al: Jump from pre-mutation to pathologic expansion in C9orf72. Am J Hum Genet. 2015 Jun 4;96(6):962-970
9. Gami P, Murray C, Schottlaender L, et al: A 30-unit hexanucleotide repeat expansion in C9orf72 induces pathological lesions with dipeptide-repeat proteins and RNA foci, but not TDP-43 inclusions and clinical disease. Acta Neuropathol. 2015 Oct;130(4):599-601
10. Ng ASL, Tan EK: Intermediate C9orf72 alleles in neurological disorders: does size really matter? J Med Genet. 2017 Sep;54(9):591-597
11. Nordin A, Akimoto C, Wuolikainen A, et al: Sequence variations in C9orf72 downstream of the hexanucleotide repeat region and its effect on repeat-primed PCR interpretation: a large multinational screening study. Amyotroph Lateral Scler Frontotemporal Degener. 2017 May;18(3-4):256-264
12. Van Mossevelde S, van der Zee J, Cruts M, Van Broeckhoven: Relationship between C9orf72 repeat size and clinical phenotype. Curr Opin Genet Dev. 2017 Jun;44:117-124

Performance

Method Description

A combined amplicon-length and repeat-primed polymerase chain reaction-based assay is utilized to size alleles up to approximately 145 repeats and detect expansions of GGGGCC hexanucleotide repeat region in the *C9orf72* gene.(Ida CM, Lundquist PA, Bram E, et al: Evaluation of Single-tube Combined Amplicon-length and Repeat-primed Long-read PCR Assay for Clinical Detection and Characterization of *C9orf72* Hexanucleotide Repeat Expansion. Abstract 731. 2017 ACMG Annual Clinical Genetics Meeting. Phoenix, AZ, March 23, 2017.)

PDF Report

No

Day(s) Performed

Tuesday

Report Available

21 to 28 days

Specimen Retention Time

Whole Blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location

Rochester

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81479

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
C9ORF	C9orf72, Molecular Analysis	81846-8

Result ID	Test Result Name	Result LOINC® Value
52852	Result Summary	50397-9
52853	Result	77635-1
52854	Interpretation	69047-9
52855	Reason for Referral	42349-1
52856	Specimen	31208-2
52857	Source	31208-2
52858	Released By	18771-6
55158	Method	85069-3