Test Definition: AFTDP

Inherited Frontotemporal Dementia and Amyotrophic Lateral Sclerosis Gene Panel, Varies

Overview

Useful For

Establishing a molecular diagnosis for patients with frontotemporal dementia (FTD) and/or amyotrophic lateral sclerosis (ALS)

Identifying variants within genes known to be associated with FTD and/or ALS, allowing for predictive testing of at-risk family members

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
_STR1	Comp Analysis using STR (Bill only)	No, (Bill only)	No
_STR2	Add'l comp analysis w/STR (Bill Only)	No, (Bill only)	No
MATCC	Maternal Cell Contamination, B	Yes	No

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 51 genes associated with frontotemporal dementia and/or amyotrophic lateral sclerosis: *ALS2, ANG, ANXA11, APP, ASAH1, CCNF, CHCHD10, CHMP2B, CSF1R, DCTN1, ERBB4, FIG4, FUS, GRN, HEXB, HNRNPA1, HNRNPA2B1, ITM2B, KIF5A, MAPT, MATR3, NEFH, NOTCH3, NPC1, NPC2, OPTN, PANK2, PFN1, PRNP, PSEN1, PSEN2, SETX, SIGMAR1, SNCA, SOD1, SPG11, SPTLC1, SQSTM1, TAF15, TARDBP, TBK1, TBP, TIA1, TIMM8A, TREM2, TUBA4A, TYROBP, UBQLN2, VAPB, VCP*, and *VRK1*. A polymerase chain reaction-based assay is utilized to detect *C9orf72* GGGGCC hexanucleotide repeat expansions. See Targeted Genes and Methodology Details for Inherited Frontotemporal Dementia and Amyotrophic Lateral Sclerosis Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for frontotemporal dementia and/or amyotrophic lateral sclerosis.

Testing Algorithm

For 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)
- Targeted Genes and Methodology Details for Inherited Frontotemporal Dementia and Amyotrophic Lateral Sclerosis Gene Panel

Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

First tier testing for a diagnosis of dementia or amyotrophic lateral sclerosis is C9ORF / *C9orf72*, Hexanucleotide Repeat, Molecular Analysis, Varies, which is included with this test but is also available separately.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies. To modify this panel via CGPH, please use the Neurologic Disorders disease state for step 1 on the custom gene ordering tool.

Specimen Required

Patient Preparation: A previous hematopoietic stem cell transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a hematopoietic stem cell transplant, call 800-533-1710.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube: Lavender top (EDTA) or yellow top (ACD)
Specimen Volume: 3 mL
Collection Instructions:

1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days

Additional Information:

1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Cord blood

Container/Tube: Lavender top (EDTA) or yellow top (ACD)

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.
2. Send cord blood specimen in original tube. Do not aliquot.

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days

Additional Information:

1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.
3. While a properly collected cord blood sample may not be at risk for maternal cell contamination, unanticipated complications may occur during collection. Therefore, maternal cell contamination studies are recommended to ensure the test results reflect that of the patient tested and are available at an additional charge. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Specimen Type: Saliva

Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.

Supplies: Saliva Swab Collection Kit (T786)

Specimen Volume: 2 Swabs

Collection Instructions: Collect and send specimen per kit instructions.

Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days

Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

Specimen Type: Extracted DNA

Container/Tube:

Preferred: Screw Cap Micro Tube, 2 mL with skirted conical base

Acceptable: Matrix tube, 1 mL

Collection Instructions:

1. The preferred volume is at least 100 mcL at a concentration of 75 ng/mcL.

2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred) 1 year/Ambient/Refrigerated
Additional Information: DNA must be extracted in a CLIA-certified laboratory or equivalent and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

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

See Specimen Required

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	Varies		

Clinical & Interpretive

Clinical Information

Frontotemporal dementia (FTD) is a progressive neurodegenerative syndrome that affects the frontal and temporal cerebral cortices. Clinical presentation is variable and includes changes in behavior, difficulties with language, rigidity, palsy, and saccadic (rapid) eye movement. Symptoms generally begin between 40 and 60 years of age, with a mean age of onset at approximately 45 years. They typically last between 5 and 10 years, progressing to severe dementia and mutism. The presentation of frontotemporal dementia may be confused with other dementias, including Alzheimer disease. It is important to distinguish between these different dementias because progression and patient management are different for the various dementias.

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease with progressive loss of upper and lower motor neurons. ALS typically presents with progressive muscle wasting, hyperreflexia, and spasticity. Death from respiratory failure usually occurs within 3 to 5 years of disease onset.

Frontotemporal dementia and ALS are thought to represent a continuous disease spectrum. However, the molecular mechanism underlying the co-occurrence of FTD and ALS remains unclear. In some individuals ALS occurs first, while in others FTD precedes ALS by several years. Between 40% and 50% of individuals with ALS present with an FTD-associated clinical phenotype.

Given the clinical overlap of FTD and ALS, this multigene panel includes genes associated with FTD and ALS.

Reference Values

An interpretive report will be provided.

C9orf72 Repeats:
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 the cutoff for pathogenicity is 100 repeats, most individuals affected with a *C9orf72*-related disorder have *C9orf72* hexanucleotide repeat expansions with hundreds to thousands of repeats.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be

considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic mutations and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent non-leukocyte reduced blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare professionals to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(1) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Richards S, Aziz N, Bale S, 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(5):405-424
2. Graff-Radford NR, Woodruff BK. Frontotemporal dementia. Semin Neurol. 2007;27(1):48-57
3. Karch CM, Wen N, Fan CC, et al. Selective genetic overlap between amyotrophic lateral sclerosis and diseases of the frontotemporal dementia spectrum. JAMA Neurol. 2018;75(7):860-875
4. Benatar M, Heiman-Patterson TD, Cooper-Knock J, et al. Guidance for clinical management of pathogenic variant carriers at elevated genetic risk for ALS/FTD. J Neurol Neurosurg Psychiatry. Published online January 31, 2025
5. Chambers C, Lichten L, Crook A, Uhlmann WR, Dratch L. Incorporating genetic testing into the care of patients with amyotrophic lateral sclerosis/frontotemporal degeneration spectrum disorders. Neurol Clin Pract. 2023;13(5):e200201

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See Targeted Genes and Methodology Details for Inherited Frontotemporal Dementia and Amyotrophic Lateral Sclerosis Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

A combined amplicon-length and repeat-primed PCR-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)

Genes analyzed: *ALS2, ANG, ANXA11, APP, ASAH1, CCNF, CHCHD10, CHMP2B, CSF1R, DCTN1, ERBB4, FIG4, FUS, GRN, HEXB, HNRNPA1, HNRNPA2B1, ITM2B, KIF5A, MAPT, MATR3, NEFH, NOTCH3, NPC1, NPC2, OPTN, PANK2, PFN1, PRNP, PSEN1, PSEN2, SETX, SIGMAR1, SNCA, SOD1, SPG11, SPTLC1, SQSTM1, TAF15, TARDBP, TBK1, TBP, TIA1, TIMM8A, TREM2, TUBA4A, TYROBP, UBQLN2, VAPB, VCP*, and *VRK1*.

PDF Report

Supplemental

Day(s) Performed

Varies

Report Available

21 to 28 days

Specimen Retention Time

Whole blood: 28 days (if available); Extracted DNA: 3 months; Saliva: 30 days (if available)

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

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

81403
81406 x 9
81404 x 3
81405 x 2
81407
81479
81479 (if appropriate for government payers)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
AFTDP	FTD and ALS Gene Panel	51966-0

Result ID	Test Result Name	Result LOINC® Value
617494	Test Description	62364-5
617495	Specimen	31208-2
617496	Source	31208-2
617497	Result Summary	50397-9
617498	Result	82939-0
617499	Interpretation	69047-9
618174	Additional Results	82939-0
617500	Resources	99622-3
617501	Additional Information	48767-8
617502	Method	85069-3
617503	Genes Analyzed	48018-6
617504	Disclaimer	62364-5
617505	Released By	18771-6