MAYO CLINIC LABORATORIES

Test Definition: APOEG

Apolipoprotein E Genotyping, Blood

Overview

Useful For

Determining the specific apolipoprotein E (APOE) genotypes in individuals with type III hyperlipoproteinemia

Determining the specific APOE genotypes that may increase risk for amyloid related imaging abnormalities in individuals being treated for Alzheimer disease with B-amyloid-targeting antibodies

APOE genotyping has been used to assess susceptibility for Alzheimer disease. However, the use of APOE analysis for predictive testing for Alzheimer disease is not currently recommended by the American College of Medical Genetics due to limited clinical utility and poor predictive value.

Special Instructions

- Informed Consent for Genetic Testing
- Molecular Genetics: Neurology Patient Information
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) including Restriction Digest

NY State Available

Yes

Specimen

Specimen Type

Varies

Specimen Required

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

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: None
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 is met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Extracted DNA
Container/Tube:
Preferred: Screw Cap Micro Tube, 2mL with skirted conical base
Acceptable: Matrix tube, 1mL
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.
-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

Apolipoproteins are structural constituents of lipoprotein particles that participate in lipoprotein synthesis, secretion, processing, and metabolism. Apolipoproteins have critical roles in blood lipid metabolism. Disease-causing variants in apolipoprotein E (*APOE*) are responsible for familial dysbetalipoproteinemia, or type III hyperlipoproteinemia, in which increased plasma cholesterol and triglycerides result from impaired clearance of chylomicron and very-low-density lipoprotein remnants. Additionally, specific *APOE* alleles are associated with risk for late-onset Alzheimer disease.

The human *APOE* gene is located on chromosome 19. The 3 common *APOE* alleles are designated e2, e3, and e4, which encode the ApoE isoforms E2, E3, and E4, respectively. E3, considered the reference allele, shows cysteine (Cys) at amino acid position 130 and arginine (Arg) at position 176 on the NP_0032 transcript. E2 and E4 differ from E3 by single amino acid substitutions at positions 176 and 130, respectively. E2 shows cysteine (Cys) at position 176 and has an estimated global minor allele frequency of 2% to 12%, depending on ancestral population. E4 shows arginine (Arg) at position 130 and has an estimated global minor allele frequency of 7% to 15%, depending on ancestral population.

E2 and E4 are both associated with higher plasma triglyceride concentrations. Over 90% of individuals with type III hyperlipoproteinemia are homozygous for the e2 allele. However, less than 10% of individuals homozygous for the e2 allele have overt type III hyperlipoproteinemia. This suggests that other genetic, hormonal, or environmental factors must contribute to the phenotypic expression of the disease. The e4 allele has been linked to pure elevations of low-density lipoproteins. Patients with a lipid profile consistent with type III hyperlipidemia are candidates for analysis of their *APOE* genotype.

The *APOE* gene is also a known susceptibility gene for Alzheimer disease. The e4 allele is associated with an increased risk for Alzheimer disease, particularly late-onset disease, in a dose-dependent manner. This risk is also influenced by other factors, including age and ancestral population/genetic background. It is estimated that individuals with the *APOE* e3/e4 genotype have a 3-fold to 4-fold relative risk for Alzheimer disease, while homozygotes for e4 allele have a 10-fold to 15-fold relative risk. Several studies have suggested a protective effect of the *APOE* e2 allele.

The *APOE* e4 allele, however, is neither sufficient nor necessary for the development of Alzheimer disease.

Approximately 50% of individuals with Alzheimer disease carry an e4 allele, and many individuals who have an e4 allele will never develop Alzheimer disease. The use of *APOE* analysis for predictive testing for Alzheimer disease in asymptomatic individuals is not currently recommended by the American College of Medical Genetics and Genomics due to limited predictive value.

Additionally, according to the US Food and Drug Administration (FDA) label, the *APOE* e4 allele has been associated with a higher incidence of amyloid-related imaging abnormalities (ARIA) in the context of amyloid-targeting antibody treatments for Alzheimer disease, including lecanemab and donanemab. For this reason, the FDA recommends genotyping for *APOE* e4 status prior to treatment in order to allow for better understanding of an individual's ARIA risk.

Reference Values

An interpretive report will be provided

Interpretation

The interpretive report includes an overview of the findings as well as the associated clinical significance.

Cautions

This assay will not detect all of the genetic variants that cause type III hyperlipoproteinemia. Therefore, the absence of a detectable genetic variant does not rule out the possibility that an individual is a carrier of or affected with this disease.

This assay cannot predict or rule out the development of Alzheimer disease in an individual.

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

Rare variants (ie, polymorphisms) exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

In rare cases, DNA alterations of undetermined significance may be identified.

This assay does not identify all of the less common apolipoprotein E alleles. Thus, an individual who appears to be homozygous for e2, e3, or e4 may carry one of the rare alleles that cannot be detected by this assay.

Clinical Reference

1. Smelt AH, de Beer F. Apolipoprotein E and familial dysbetalipoproteinemia: Clinical, biochemical, and genetic aspects. Semin Vasc Med. 2004;4(3):249-257
2. Utermann G. Morgagni lecture: genetic polymorphism of apolipoprotein E-impact on plasma lipoprotein metabolism. In: Crepaldi G, Tiengo A, Baggio G, eds. Diabetes, Obesity and Hyperlipidemias 3: Proceedings of the 4th European Symposium on Metabolism. 1985. Elsevier; 1-28
3. Elosua R, Ordovas JM, Cupples LA, et al. Association of APOE genotype with carotid atherosclerosis in men and women: the Framingham Heart Study. J Lipid Res. 2004;45(10):1868-1875
4. Poirier J, Davignon J, Bouthillier D, et al. Apolipoprotein E polymorphism and Alzheimer's disease. Lancet. 1993;342(8873):697-699
5. Farrer L, Cupples A, Haines J, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. JAMA. 1997;278(16):1349-1356
6. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011;13(6):597-605
7. American College of Medical Genetics and Genomics: Five things physicians and patients should question. Choosing Wisely; 2015. Updated July 1, 2021. Accessed January 16, 2025. Available at www.choosingwisely.org/societies/american-college-of-medical-genetics-and-genomics/
8. Filippi M, Cecchetti G, Spinelli EG, Vezzulli P, Falini A, Agosta F. Amyloid-Related Imaging Abnormalities and B-Amyloid-Targeting Antibodies: A Systematic Review. JAMA Neurol. 2022;79(3):291-304
9. LEQEMBI (lecanemab-irmb injection, for intravenous use). Package insert: Eisai Inc; Revised 07/2023. Available at www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf
10. KISUNLA (donanemab-azbt injection, for intravenous use). Package insert: Eli Lilly and Company; Revised 07/2024. Available at www.accessdata.fda.gov/drugsatfda_docs/label/2024/761248s000lbl.pdf
11. Kane M. Lecanemab Therapy and APOE Genotype. In: Pratt VM, Scott SA, Pirmohamed M, et al, eds. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012. Updated August 12, 2024. Accessed January 16, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK605938/
12. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2023;10(3):362-377. doi:10.14283/jpad.2023.30

13. Belloy ME, Andrews SJ, Le Guen Y, et al. APOE genotype and Alzheimer disease risk across age, sex, and population ancestry. JAMA Neurol. 2023;80(12):1284-1294. doi:10.1001/jamaneurol.2023.3599

Performance

Method Description
A polymerase chain reaction-based assay, which includes HhaI digestion of the amplified product, is utilized to identify the 3 most common apolipoprotein E alleles (e2, e3, e4).(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Tuesday, Thursday

Report Available
6 to 7 days

Specimen Retention Time
Whole blood: 30 days (if available); Extracted DNA: 3 months

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
81401-*APOE (apolipoprotein E)* (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
APOEG	Apolipoprotein E Genotyping, B	42315-2

Test Definition: APOEG

Apolipoprotein E Genotyping, Blood

Result ID	Test Result Name	Result LOINC® Value
53198	Result Summary	50397-9
53199	Result	42315-2
53200	Interpretation	69047-9
53201	Reason for Referral	42349-1
53202	Specimen	31208-2
53203	Source	31208-2
53204	Released By	18771-6