Apolipoprotein E (ApoE) - A Genetic Risk Marker for Alzheimer's Disease

PrecivityAD™

What is Apolipoprotein E (ApoE)?

Apolipoprotein E (ApoE) is a protein involved in the metabolism of fats (lipids) in the body. It is a component of lipoproteins – particles that transport fats such as cholesterol and triglycerides through the bloodstream. In the circulation, ApoE is part of several classes of lipoprotein particles, including: chylomicron remnants, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and high-density lipoprotein (HDL)[1]. It is highly expressed in the liver and in the brain[1]. The ApoE gene exists as three main forms – ApoE2, ApoE3 and ApoE4. An individual inherits one copy of the ApoE gene from his/her mother and a second copy of the ApoE gene from father. This gives rise to the common ApoE genotypes found in people, 22 (e.g., two copies of the ApoE2 gene), ε32, ε33, ε42, ε43 and ε44[2]. The ApoE ε3 allele is the most frequent in all populations, with a frequency range of 50-90%. ApoE ε4 and ApoE ε2 allele frequencies range from 5-35% and 1-5%, respectively[3].

Genetically, the ApoE4 form of the ApoE gene is the strongest risk factor for the most common form of Alzheimer's disease, known as late-onset Alzheimer's disease[4,5]. Individuals with one copy of ApoE4 have a threefold higher risk, while those who inherit two copies of ApoE4 have an eight to 12-fold greater risk of developing Alzheimer's dementia compared to ApoE4 non-carriers. ApoE2 individuals have lower risk for developing late-onset Alzheimer's[3-7]. ApoE forms behave differently with regards to their influence on the buildup of amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the brain, the pathological hallmarks of Alzheimer's disease.

The ApoE4 genotype is a significant risk factor for brain amyloid accumulation[7-8]. Many epidemiology studies from various populations have confirmed the increased frequency of ApoE4 in late-onset Alzheimer's disease patients compared to ApoE4 non-carriers, though the frequency varies in different ethnicities[3]. **It is important to note that ApoE4 is neither necessary nor sufficient for the development of Alzheimer's disease so ApoE genetic information alone cannot be used to determine the presence of Alzheimer's disease.** A person's overall risk for developing Alzheimer's disease depends on many genetic, biochemical, epigenetic, and environmental factors.

The ApoE2 genotype has been shown to increase the risk of hyperlipoproteinemia type III, a rare genetic disorder that results from impaired clearance of chylomicron and VLDL remnants in blood[9-10]. The risk for developing coronary heart disease (CHD) is five to ten times higher for an individual with hyperlipoproteinemia type III compared to the general population. The presence of ApoE2 genes by itself usually does not result in the development of symptoms of hyperlipoproteinemia type III[11]. Additional genetic, environmental, or hormonal factors play a role in the development of the disorder[11]. The ApoE genotype differs in fat metabolism where ApoE2 is associated with lower cholesterol levels than Apo3 and ApoE4; and ApoE4 is associated with higher cholesterol levels[11]. Data from epidemiologic studies show that the relationship between ApoE genotypes and coronary heart disease (CHD) outcomes are conflicting, despite well-established differences in fat metabolism by ApoE genotype[12-14].

What are the possible ApoE test results and what does the test result mean?

After ApoE testing, there are six possible allele combinations: ApoE2/ApoE2, ApoE2/ApoE3, ApoE2/ApoE4, ApoE3/ApoE3, ApoE3/ApoE4, and ApoE4/ApoE4.

APOE2/APOE2: Individuals with an ApoE2/ApoE2 genotype have only ApoE2 proteins present in the blood and this genotype is associated with a **decreased** risk for Alzheimer's disease compared to common allele ApoE3/ApoE3 and ApoE4 carriers.

ApoE2/ApoE3: Individuals with an ApoE2/ApoE3 genotype have ApoE2 and ApoE3 proteins present in the blood and this genotype is associated with a **decreased** risk for Alzheimer's disease compared to common allele ApoE3/ApoE3 and ApoE4 carriers.

ApoE2/ApoE4: Individuals with an ApoE2/ApoE4 genotype have ApoE2 and ApoE4 proteins present in the blood. One copy of ApoE4 in this genotype is associated with **increased** risk for Alzheimer's disease as compared to common allele combinations such as ApoE3/ApoE3, ApoE2/ApoE2, and ApoE2/ApoE3.

APOE3/APOE3: Individuals with an ApoE3/ApoE3 genotype only have ApoE3 proteins present in the blood. This genotype has **decreased** risk for Alzheimer's disease as compared to genotypes with ApoE4 carriers and increased risk as compared to ApoE2/ApoE2 and ApoE2/ApoE3 genotypes.

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APOE3/APOE4: Individuals with ApoE3/ApoE4 genotype have ApoE3 and ApoE4 proteins present in the blood. One copy of ApoE4 in this genotype is associated with approximately threefold **increased** risk for Alzheimer's disease as compared to ApoE4 non-carriers.

APOE4/APOE4: Individuals with an ApoE4/ApoE4 genotype have ApoE4 proteins present in the blood. Two copies of ApoE4 in this genotype is associated with approximately eight to twelve-fold **increased** risk for Alzheimer's disease compared to ApoE4 non-carriers.

Can the ApoE genotyping test diagnose Alzheimer's disease in a person with symptoms of cognitive impairment or early dementia?

No. ApoE is known as a susceptibility gene, not a deterministic one. In people with symptoms, only about 60% of those with late onset Alzheimer's disease will carry an ApoE4 gene. ApoE4 is neither necessary nor sufficient for the development of Alzheimer's disease. Thus, ApoE genetic information alone cannot be used to identify the presence of Alzheimer's disease. Further, the use of ApoE analysis alone to predict Alzheimer's disease is not currently recommended by the American College of Medical Genetics due to the poor predictive value of only measuring ApoE.

Why does the PrecivityAD™ test have ApoE proteotype (equivalent to ApoE genotype) included as a measurement along with Aβ42/40 ratio to determine Alzheimer's pathology?

The PrecivityAD™ test measures the concentrations of amyloid beta 42 and 40 (Aβ42 and Aβ40), as well as the presence of apolipoprotein E (ApoE) isoforms in the blood. The test indicates if an individual is likely to have amyloid plaques in the brain, a hallmark of Alzheimer's disease. ApoE4 genotype is a significant risk factor for amyloid accumulation in the brain and Alzheimer's disease, and its incorporation into C_2N's proprietary algorithm increases the accuracy of the test. Using data from 686 patients, an algorithm based on plasma Aβ42/40 ratio, ApoE genotype, and patient age improved the accuracy of the prediction between amyloid PET positive versus amyloid PET negative patients, as compared to using the Aβ42/40 ratio alone.

What should my patient do before and after getting the PrecivityAD™ test or Precivity-ApoE™ test?

Your patient or your patient's family members can order the PrecivityAD™ test or Precivity-ApoE™ test. In view of the increased risk of Alzheimer's disease associated with the ApoE4 genotype, your patient or your patient's family members might find it concerning if your patient were to receive an ApoE4 positive test result. You can talk to your patient about genetic testing and how to obtain genetic counseling. General information and resources on genetic testing can be found at https://precivityad.com/resources. Further, C_2N recommends that patients consult with a medical geneticist or genetic counselor and /or a physician after the test is completed.

What are the limitations of the ApoE Proteotyping test?

C_2N's ApoE proteotyping test detects only peptides from ApoE2, ApoE3 and ApoE4 proteins and does not detect peptides from very rare ApoE proteoforms (e.g. ApoE1, ApoE5, and ApoE7). False positive or false negative blood test results may occur. A diagnosis of Alzheimer's disease as the underlying cause for an individual's clinical presentation should always be considered in the context of that individual's medical and family history and physical, neurological examination and biomarker evaluations.

References: 1. Mahley RW, Rall SC Jr. Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet. 2000; 1:507–37. **2.** G. Utermann, M. Hees, A. Steinmetz, Polymorphism of apolipoprotein E and occurrence of dysbetalipoproteinaemia in man Nature, 269 (1977), pp. 604-607. **3.** Verghese PB, Castellano JM, and Holtzman DM, Roles of Apolipoprotein E in Alzheimer's disease and Other Neurological Disorders. Lancet Neurol. 2011 March; 10(3): 241–252. **4.** Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993; 261:921–3. **5.** Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology. 1993; 43:1467–72 **6.** Roses AD. Apolipoprotein E alleles as risk factors in Alzheimer's disease. Annu Rev ed. 1996; 47:387–400 **7.** Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. Neuron. 2009; 63:287–303 **8.** Liu CC1, Liu CC, Kanekiyo T, Xu H, Bu G.Apolipoprotein E and Alzheimer's disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013 Feb;9(2):106-18. doi: 10.1038/nrneurol.2012.263. Epub 2013 Jan 8. **9.** Smelt AH, de Beer F: Apolipoprotein E and familial dysbetalipoproteinemia: Clinical, biochemical, and genetic aspects. Semin Vasc Med 2004;4(3):249-257 **10.** Utermann G: Morgagni lecture: genetic polymorphism of apolipoprotein E-impact on plasma lipoprotein metabolism In Diabetes, Obesity and Hyperlipidemias. Edited by G Crepaldi, A Tiengo, G Baggio. Amsterdam. Elsevier, 1985, pp 1-28 **11.** R W Mahley, Y Huang, S C Rall Jr. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia): questions, quandaries, and paradoxes, J Lipid Res. 1999 Nov;40(11):1933-49. **12.** 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 **13.** Heather Ward Ward H, Mitrou PN, Bowman R, Luben R, Wareham NJ, Khaw KT, Bingham S, APOE genotype, lipids, and coronary heart disease risk: a prospective population study Arch Intern Med. 2009 Aug 10;169(15): 1424-9. **14.** Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC, Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol. 2002 Mar 15;155(6):487-95