

1. Genetic Tests

1. Apo E

CPT Code

83891 isolation; 83908 amplification x 2; 83892 enzyme digestion x 4; 83903 x2 mutation scanning; 83896 x4 nucleic acid probes; 83912 interpretation and report - Additional CPT code modifiers may be required for procedures performed to test for oncologic or inherited disorders.

Test Description

Apo E is a polymorphic glycoprotein found (often in multiple copies) on plasma lipoproteins including chylomicrons, very low density lipoprotein (VLDL), chylomicron and VLDL remnant lipoproteins and high density lipoproteins (HDL). It is not present on LDL particles. Different Apo E isoforms alter plasma lipoprotein concentrations because they have different affinities for various membrane receptors and lipases. This phenotypic expression different isoforms vary according to various environmental stimuli or genetic associations. Apo E has two primary metabolic roles involving its receptor-binding and lipid-binding functions: 1) transport of neural lipids from their site of synthesis, or absorption, to the tissues where lipids are stored, metabolized or excreted, and 2) delipidation and transport of neutral lipids, in particular cholesterol, from the peripheral organs to the liver for excretion. Apo E also modulates the activity of enzymes involved in lipid and lipoprotein metabolism such as hepatic lipase (HL), lipoprotein lipase (LPL), cholesterol ester transfer protein (CETP) and lecithin: cholesterol acyltransferase (LCAT).¹

The human apo E gene has three common alleles ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) coding for the Apo E protein as three isoforms (E2, E3, and E4), which vary in the amino acids present at position 112 and 158 of the protein. There are three homozygous (E4/E4, E3/E3, and E2/E2) and three heterozygous (E4/E3, E4/E2, and E3/E2) genotypes and phenotypes, resulting from simple co-dominant Mendelian inheritance of the Apo E gene. The Apo E genotypes include Apo E2 (E2/E2, E2/E3), Apo E3 (E3/E3, E2/E4), and Apo E4 (E3/E4; E4/E4).

Clinical Interpretation

In the clinical setting Apo E has isoform-specific roles acting at both cellular and molecular levels. Multiple studies have examined gene-drug, gene-diet and/or additional gene-environment interactions and their direct correlation with changes in plasma lipid levels, in particular recognizing the influence of the apolipoprotein E genotype (Apo E genotype).⁶

Apolipoprotein E (apoE) plays a key role in the delipidation of Apo B-containing lipoproteins and lipidation and clearance of HDL's and their core lipids. Apo E serves as a receptor-binding ligand mediating the clearance of chylomicron and remnants of very-low-density lipoprotein cholesterol from plasma.¹⁻⁴ Apo E binds to lipids, heparan sulfate proteoglycans, VLDL receptors in myocytes and adipocytes and LDL receptors. Differences in Apo E isoform receptor-binding affect plasma lipid levels. This modulates lipoprotein levels by influencing the lipolytic conversion, triglyceride-rich VLDL production and clearance rate.²

A common polymorphism in the Apo E gene (NCBI Entrez Gene 348) that codes for the 3 common isoforms E2, E3, and E4 has been studied extensively. In general, Apo E2 and Apo E4 have opposing effects on plasma lipids. Mechanistically, Apo E2 is associated with slow conversion of intermediate density lipoprotein (IDL) to LDL leading to a decrease in plasma cholesterol and increased triglycerides. Apo E3 has “normal” lipid metabolism, thus no genotype impact. Apo E4 confers a limitation of HDL binding and the normal clearance process is inhibited leading to an increase in total cholesterol, LDL and TG. Apo E2 has markedly decreased LDL-receptor binding affinity as compared with Apo E3, and some reports suggest that Apo E4 has increased affinity as compared with Apo E3.³ The binding of Apo E to lipoproteins is also isoform dependent with Apo E4 preferentially binding to VLDL and Apo E3 and Apo E2 binding to the smaller, phospholipid-rich HDL.⁴ This complex interaction generally leads to a decrease in LDL-C and HDL-C in Apo E2 compared to Apo E3 and elevated LDL-C and lowered HDL-C in Apo E4.⁵ It has been proposed that the mechanism responsible for this effect is defective binding at lipoprotein receptors noted among E2 carriers,^{47,49} which results in decreased cholesterol delivery to the hepatocytes and a subsequent upregulation of hepatic sterol synthesis and LDL receptors.⁵⁰ Conversely, the relatively stronger binding to lipoprotein receptors observed in E4 carriers increases the delivery of cholesterol to the hepatocytes,^{47,49} which may result in the downregulation of hepatic sterol synthesis, a decrease in LDL receptors, and a consequent increase in blood LDL-C concentrations.⁴

Compared with E3 homozygotes, carriers of the E2 allele, which has defective receptor-binding ability, have increased levels of ApoE and decreased LDL-C, and higher triglyceride levels, whereas carriers of the E4 allele tend to have decreased ApoE, higher plasma levels of total cholesterol, LDL-C and increased high-density lipoprotein cholesterol (HDL-C) levels.^{29, 30, 35} These patients are predisposed to an exaggerated elevation of LDL-C when their diet is high in saturated fat. It has been estimated that between 1% and 8% of variation in LDL-C level can be accounted for by APOE genotype.^{30, 31} Recent evidence also indicates that apoE may play additional roles in the development of coronary heart disease (CHD) through macrophage cholesterol efflux, platelet aggregation, and allele-specific antioxidant and immune activities.^{30, 35, 36}

The results of epidemiologic studies that examined the relationship between APOE genotypes and CHD outcomes are inconsistent, despite well-established differences in lipid metabolism by APOE genotype. Earlier meta-analyses of published studies pointed more strongly to increased CHD risk among E4 carriers, with no association noted for E2 carriers.^{5,6,33,34} More recently, a meta-analysis of 17 published and previously unpublished studies with relatively large sample sizes indicated that the risk of coronary disease was decreased among carriers of the E2 allele and marginally increased among E4 carriers.⁵¹ In the largest study cohort, the EPIC-Norfolk cohort, ApoE genotype data was examined for 22,169 men and women, APOE genotype information indicated that CHD risk was associated with APOE genotype. Variation in serum cholesterol level according to APOE genotype is well established and appeared to be the main cause of attenuation of the association between CHD and APOE relative to models without the LDL-C:HDL-C ratio. Because the possibility of residual confounding cannot be ruled out, APOE may be related to CHD through factors in addition to the LDL-C: HDL-C ratio.

Angiographic studies of CHD patients have shown that Apo E4 carriers more often have disseminated and severe coronary lesions than noncarriers.⁵⁴ The Apo E genotype is reported to increase an individual carrier’s differential susceptibility to CAD events. In larger studies and pooled analyses, Apo E4 is associated with increased CAD events compared to Apo E2 and Apo E3. Reported CAD event risk is increased about 40% in Apo E4 individuals.¹⁶ A substudy of the Scandinavian Simvastatin Survival Study (4S) looked at 966 patients with CAD.¹⁷ Apo E4 subjects who received placebo versus simvastatin had increased risk of CAD-related death (odds ratio - 1.8) compared to non-Apo E4 individuals. A case control

analysis of 619 subjects from the Multiple Risk Factor Intervention Trial (MRFIT) found the Apo E4 genotype associated with increased risk for non-fatal myocardial infarction and CAD-related death, even after adjustment for differences in LDL-C, HDL-C, body mass index, and smoking and diastolic blood pressure.²⁷

Treatment Considerations

In a clinical model where Apo E genotype in combination with a stressed environment drives the phenotypic expression of lipid abnormalities, numerous studies looking at gene-environment interaction and the resultant effect on lipid metabolism provide data to assist in developing therapeutic recommendations that target improvements in abnormal lipid levels, consistent with existing benefits traditional lipid guideline related studies.

Identifying the specific genotype in a particular patient allows modification of proper lipid-lowering treatment recommendations for CVD, including lipid-lowering drugs, food intake and alcohol use. Where drug therapy is needed, the genotype information can provide more rational use of an appropriate drug and/or dose for certain Apo E genotypes. Without Apo E genotype information, a significant percentage of patients could be suboptimally treated. It is much better to know your enemy and the specific information gleaned from Apo E genotype testing will augment physician efforts to aggressively treat cardiovascular disease.

The Apo E genotype directly influences variations in lipid metabolism and is correlated, under environmental stress, with the phenotypic expression of CVD states consistent with these metabolic differences.^{1, 41} Interactions between Apo E gene polymorphisms, abnormal lipid profiles and diet and drug therapies are now well documented. Understanding and identifying these gene-environment interactions can influence a therapeutic regimen to better treat dyslipidemias and the associated atherosclerotic cardiovascular disease process. Therapy targeting the lipid abnormalities resulting from the phenotypic expression of certain Apo E genotypes in response to environmental stress factors can mediate their impact on CVD.^{65,67,68,70,72}

Current dietary recommendations for reducing CVD target atherosclerotic associated diseases such as hypertension, dyslipidemias, obesity and diabetes tend to be broad-based and generic, targeting fat, cholesterol and often sodium restriction. General “guidelines” are applied in a “one-size-fits-all” style for a consensus, at-risk population. In a broad sense, the effectiveness of this approach appears limited, which cannot be explained merely by personal non-adherence to guideline recommendations. An important reason to explain this limitation emerges from studies demonstrating that dietary changes induce a lipid response that varies between individuals (interindividual variability), due to effects of age, gender, ethnicity and genetic heterogeneity, including gene polymorphisms.¹³ The American Heart Association’s (AHA) Dietary Guidelines (Revision 2006) specifically references the need to consider how underlying genetic and metabolic heterogeneity may limit the potential for generalized nutritional guidelines to address individual dietary responsiveness.¹⁵ In their Scientific Conference proceedings on preventive nutrition, the AHA has also emphasized the need for focusing on the influence of gene polymorphisms on individual responses to dietary factors.¹⁶ While a healthy lifestyle is recommended for all patients, this may be particularly relevant for Apo E, recognizing the associated variable lipid-lowering response to dietary fat restriction associated with different Apo E genotypes. Reports note marked variability in the LDL-C lowering response to a restricted fat diet,¹⁷⁻¹⁹ which has been particularly ascribed to Apo E gene polymorphisms.^{20, 21} Specifically, current recommendations for “standard”

cardiac diets are not sufficient in lowering CVD potential in CVD-susceptible, but diet-hypo-responsive, individuals.

The NCEP Guidelines consider lowering LDL-C with statins as a treatment of choice for CVD. Statins, however, are not sufficient therapy in some susceptible individuals due to a wide variability in lipid-lowering drug response, in part related to Apo E genotype influence.¹⁰ This is consistent with the partial CVD event reduction (25-35%) seen in the large statin trials. As example, pertinent to generally accepted considerations for broad-based statin use to treat elevated LDL-C, subjects carrying the E4 allele are poor responders to lipid-lowering drugs,^{10, 11, 12} except for probucol¹² and possibly simvastatin,¹⁴ in contrast to low fat dietary responsiveness.¹²

Smoking is a major environmental risk factor influencing CVD,²² associated with a 2-fold lifetime CVD risk,²³ yet disease develops earlier in some smokers whereas other smokers appear relatively unaffected. An individual's genotype, particularly the Apo E genotype, can affect a variable response to the negative environmental impact of smoking relevant to coronary heart disease and effects on intermediate lipid traits. Apo E4 smokers are reported to have a particularly high CVD risk compared with Apo E4 non-smokers.^{6, 24} The additional benefit of smoking cessation is emphasized in that former Apo E4 smokers also have a lower CVD risk compared to smokers. Another study analysis showed that compared to Apo E3 individuals, the Apo E4 genotype incurred more than an additive interaction between smoking and genotype with a much higher CVD risk.²⁵ The more than additive interaction between Apo E4 smokers and CVD was also found in an analysis of the Framingham Offspring data.

Apo E Genotype Response Summary

Inherited Trait	Therapeutic Options		
ApoE Genotype			
<ul style="list-style-type: none"> Produced primarily in the liver and brain, ApoE transports lipids to the tissues for storage Transports cholesterol and other lipids from the tissues to the liver for excretion 			
ApoE4 (3/4, 4/4, 2/4) Estimated Frequency in Humans: 3/4 =25%, 4/4 =1-2%, 2/4 =1-2%			
Associations <ul style="list-style-type: none"> High risk for CVD Lower HDL-C and HDL2 Increased triglycerides Alzheimer's syndrome 	<ul style="list-style-type: none"> Increased LDL-C / increased sdLDL Increased total cholesterol More severe coronary lesions 	Lifestyle <ul style="list-style-type: none"> Very low-fat diet (will decrease LDL-C & sdLDL) Alcohol cessation recommended - alcohol decreases HDL-C/HDL2 & increases sdLDL Smoking cessation (very important for E4 genotypes) Exercise 	Medications <ul style="list-style-type: none"> Plant sterols Soy protein Soluble fiber Fish oil (can suppress HDL-C & HDL2, & raise calculated LDL-C) Less response to Statins (Simvastatin may be a better statin choice)
ApoE2 (2/2 & 2/3) Estimated Frequency in Humans: 2/2 =1-2%, 2/3 =15%			
Associations <ul style="list-style-type: none"> Increased total cholesterol Increased triglycerides Increased VLDL 	<ul style="list-style-type: none"> Decreased LDL-C Decreased HDL-C & HDL2 	Lifestyle <ul style="list-style-type: none"> Alcohol (increases HDL-C & decreases LDL-C) Moderate-fat diet (≈ 35% fat) Exercise Smoking cessation 	Medications <ul style="list-style-type: none"> Plant sterols Soy protein Soluble fiber Fish oil (decrease TRIG) Statins

ApoE3 (3/3) Estimated Frequency in Humans: 3/3 =55%



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