

# TESTING FACTS: APOLIPOPROTEIN E

## Description

Apolipoprotein E (apoE) is a multifunctional protein that plays a key role in lipoprotein metabolism and cardiovascular disease. The primary metabolic role of apoE is to transport cholesterol from the cells in the blood vessel wall to the liver for excretion. Two amino acid substitutions in the apoE structure result in three forms of apoE protein that differ in structure and function. These differences are associated with dissimilar disease risk and treatment outcomes. Incorporating a patient's apoE genotype into diagnostic and treatment protocols may guide therapy and improve patient outcomes.

## Functions of Apolipoprotein E

- ApoE is a constituent of triglyceride rich chylomicrons, VLDL and their remnants and HDL.
- The protein is involved in the efficient hepatic uptake of lipoprotein particles, stimulation of cholesterol efflux from macrophage foam cells in atherosclerotic lesions, and the regulation of immune and inflammatory responses.
- ApoE functions as a ligand for lipoprotein receptors and modulates lipoprotein levels by influencing the cholesterol clearance rate.
- Isoform specific variations (apoE 2, 3 or 4) include lipid and receptor binding differences that produce a difference in how lipids are metabolized.

## Clinical Implications

- There is a linear relationship of apoE genotypes with LDLc and coronary risk:
  - ◊ 2/2, 2/3, 2/4, 3/3, 3/4, 4/4
- ApoE2 is associated with a 20% lower risk of CAD and apoE4 is associated with a slightly higher risk of CAD compared to apoE3.
- Lower plasma levels of apoE inhibit normal lipid metabolism.

- ApoE4 individuals have greater intestinal absorption and delayed clearance of cholesterol leading to elevated LDLc and apoB levels.
- ApoE2 individuals may have weaker LDL receptor binding capacity which delays clearance of VLDL and remnants in the plasma.
- ApoE 2/2 genotype is associated with the genetic disorder type III hyperlipidemia and the risk of premature cardiovascular disease.
- ApoE genotype is a genetically fixed characteristic. It need only be determined once.

## Treatment Implications

### Lifestyle

- ApoE4 individuals may have significantly greater LDLc reduction in response to low fat diet than those with apoE3/3 genotype.
- The potential for an apoE2/2 to develop type III hyperlipidemia is largely dependent on environmental issues such as body fat and diets high in simple carbohydrates.
- ApoE3 or apoE2 individuals may have more favorable changes in lipids from exercise compared to apoE4 individuals.

### Pharmacologic Implications

- ApoE4 individuals may have less LDLc reduction on statin therapy than apoE3s or E2s, but have equivalent CAD risk reduction.
- The LDLc response to omega-3 fish oil may be dose dependent in apoE4s.

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## Apolipoprotein E Gene-Environment Interactions

ApoE Isoform	ApoE2			ApoE3	ApoE4	
	2/2	2/3	2/4	3/3	3/4	4/4
Frequency <sup>1,2,3,4</sup>	Least frequent			Most frequent (> 60%)	Moderate frequency	
CVD Risk <sup>1,2,3,4</sup>	2/3: 20% reduced 2/2: risk of type III hyperlipidemia 2/4: not well studied			Normal risk	Increased risk	
Plasma apoE levels <sup>5,6</sup>	Higher than E3			Normal levels	Lower levels than E3	
Binding properties <sup>5,6</sup>	Prefers binding with HDLc			Prefers binding with HDLc	Prefers binding with VLDL and remnants	
Mechanisms effecting lipid levels <sup>5,6</sup>	Defective LDL receptor binding			Normal LDL receptor binding	Normal LDL receptor binding	
Lipid levels differences compared to apoE 3/3 <sup>1,2,5,7,8</sup>	Increase in triglycerides, VLDL and remnants. Lowest LDLc			Normal	Increase in LDLc, small dense LDL particles, apoB and triglycerides. Decrease in HDLc	
Response to low-fat diet < 30% <sup>5,7</sup>	Least significant decrease in LDLc and apoB			Normal	Most significant decrease in LDLc and apoB	
Response to statins <sup>1,6,9,10</sup>	Greatest reduction in LDLc			Normal	Least LDLc reduction but similar CAD risk reduction as E3/3	
Response to omega-3 fish oil <sup>11,12</sup>	Triglyceride reduction			Triglyceride reduction	Triglyceride reduction LDLc change may be dose dependent	
Response to moderate alcohol <sup>13</sup>	Decreased LDLc in men			No change in LDLc in men	Increased LDLc in men	
Increased risk for carotid atherosclerosis due to smoking <sup>14</sup>	1.7-fold increased risk			1.7-fold increased risk	3.7-fold increased risk	
Response to exercise training <sup>5,15</sup>	Significant improvement in lipids			Significant improvement in lipids	Least significant improvement in lipids	

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