High cholesterol and the APOE gene

APOE4 carriers are prone to high cholesterol and Alzheimer's disease. Low-fat diets can help reduce the risk for these diseases. APOE4 is more common (20-30% occurrence) in Africans and Caucasians than in other ethnic groups.

High blood cholesterol is a major risk factor for cardiovascular diseases. Genetic variations in the APOE gene predispose people to different levels of blood cholesterol in response to dietary fat.

[click to enlarge]

There are three common variants of the APOE gene: E2, E3, and E4. Since human cells have two copies of each gene, there are six APOE genotypes: E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, and E4/E4. The E3/E3 genotype is the most common and found in about 60% of the human population. This genotype is associated with a normal level of blood cholesterol.

The distributions of E2, E3 and E4 are different in human populations. American Indians, Asians and Mexican Americans have the highest frequency of E3 (> 84%); Africans and African Americans have the

highest frequency of E4 (20.1% and 31% respectively); and African Americans and Caucasians (except Finns) have the highest frequency of E2 (7.3 to 13.1%).

Table 1. Apo E gene and genotype frequency in human population (adapted from Eichner et al, 2002. Am J Epidemiol 155:487–95).

Population	Gene Frequency			Genotype Frequency					
	E2	E3	E4	E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
African Americans	13.1%	66.8%	20.1%	2.0%	18.0%	6.0%	43.0%	28.0%	3.0%
Africans (Nigerians)	2.8%	66.2%	31.0%	0.0%	3.0%	3.0%	46.0%	37.0%	11.0%
American Indians (men)	1.7%	85.0%	13.3%	0.0%	3.0%	0.5%	71.6%	23.9%	1.2%
American Indians (women)	1.6%	85.8%	12.6%	0.1%	2.6%	0.5%	73.2%	22.7%	1.0%
Caucasians (Finland)	3.9%	76.7%	19.4%	0.3%	5.4%	1.8%	58.7%	30.6%	3.2%
Caucasians (France)	8.1%	80.2%	11.7%	0.8%	13.1%	1.6%	64.3%	18.7%	1.6%
Caucasians (Germany)	8.2%	78.2%	13.6%	0.9%	11.7%	2.9%	62.2%	19.9%	2.2%
Caucasians (Italy)	7.3%	82.7%	10.0%	0.4%	12.0%	16.5%	68.4%	1.5%	1.2%
Caucasians Americans (men)	8.3%	78.5%	13.1%	0.9%	12.9%	1.9%	62.9%	18.3%	3.0%
Caucasians Americans (women)	7.7%	78.9%	13.3%	0.3%	13.3%	1.4%	62.6%	19.3%	3.0%
Chinese	7.4%	84.4%	8.2%	1.4%	12.1%	0.0%	70.9%	14.9%	0.7%
Japanese	3.7%	84.6%	11.7%	0.3%	6.1%	0.7%	71.9%	19.3%	1.7%
Mexican Americans	3.9%	85.9%	10.2%	0.2%	6.7%	0.7%	73.8%	17.3%	1.1%

In general, E2 carriers are associated with low LDL cholesterol and low incidence of coronary heart disease. But in the presence of other environmental or genetic factors, carriers of the E2/E2 genotype are also prone to a severe disease called type III hyperlipoproteinaemia. In contrast, E4 carriers are prone to high LDL cholesterol, coronary heart disease, atherosclerosis and Alzheimer's disease.

Table 2: Determine your APOE status using SNPs rs429358 and rs7412

rs429358	rs7412	APOE Status
TT	TT	E2/E2
TT	CT	E2/E3
CT	CT	E2/E4
TT	CC	E3/E3
CT	CC	E3/E4
CC	CC	E4/E4

* Each of us have two copies of the APOE gene: one from our mother and one from our father. Therefore, we can have two different APOE alleles.

The risks associated with these genotypes are gene dose-dependent. Genotypes E2/E2 and E4/E4 represent two extreme situations while E2/E4 behaves very similarly to E3/E3. The risks associated with E2/E3 are

between that of E2/E2 and E3/E3; the risks associated with E3/E4 are between that of E3/E3 and E4/E4.

The differing risks for high blood cholesterol are the result of the enzymatic activity associated with the variants. The APOE gene makes the protein apolipoprotein E (Apo E) which is involved in the production, delivery, and utilization of cholesterol in the body. The E2 variant makes a protein characterized by slower cholesterol metabolism, which results in a lower blood cholesterol. In contrast, the E4 variant makes a protein characterized by faster cholesterol metabolism resulting in a higher blood cholesterol level.

Since high fat diets often lead to high cholesterol, low-fat, high-carb diets are recommended for E4 carriers while high-fat, low-carb diets are recommended for E2 carriers. Extensive research on APOE variants and dietary interactions has allowed us to better understand the dietary and lifestyle requirements for carriers of all genotypes (Table 3). Please use these recommendations wisely and factor in your personal health status and lifestyle. For example, if you are an E2 carrier but have high cholesterol due to other reasons, you certainly don't want to follow a high-fat diet.

Table 3. General dietary and exercise guidelines for all Apo E genotypes under normal physiological condition (2,400 kcal calorie intake per day).

Recommendations		Genotype					
		E2/E2	E2/E3	E3/E3	E2/E4	E3/E4	E4/E4
Energy source	Fat	35%	30%	25%	25%	20%	20%
	Protein	15%	15%	20%	20%	25%	25%
	Carbohydrate	50%	55%	55%	55%	55%	55%
Exercise	Aerobic	55%	55%	50%	50%	75%	75%
	Anaerobic	45%	45%	50%	50%	25%	25%
Alcohol, moderate amount		Beneficial			Harmful		

*People with medical conditions should seek guidance from their health provider when developing diet and exercise compatible regimens.

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Apo E was discovered in 1970s as a component of lipoproteins. Lipoproteins are the transportation vehicles of fatty acids and cholesterol in human blood circulation. Under normal physiological conditions, fatty acids and cholesterol are essential components of cell membranes, precursors for steroid hormones, vitamin D and bile acids, and play crucial roles in the function of the central nervous system. Lipoproteins distribute fatty acids and cholesterol to various tissues for their routine function and transport the unused portions to liver for catabolism. There are many kinds of lipoproteins in human blood circulation. They differ in size, origin, function and composition. The major types of lipoproteins include: chylomicrons, VLDL (very low density lipoprotein), LDL (low density lipoprotein) and HDL (high density lipoprotein). All of them contain Apo E, which regulates the metabolism of lipoproteins in several aspects.

First, Apo E mediates the interaction of lipoproteins with cell surface receptors in different tissues, thus determines where fatty acids and cholesterol need to be delivered to. Second, Apo E modulates the activity of lipoprotein lipase, an enzyme that frees fatty acids and cholesterol from lipoproteins at the site of delivery, thus controlling the rate of delivery. Third, Apo E has recently been shown to stimulate VLDL production by the liver, which is also associated with increased VLDL and plasma triglyceride levels. Finally, Apo E plays critical roles in regulating brain Aβpeptides level in brain. Accumulation of Aβ peptides is a hallmark of Alzheimer's disease.

The fundamental difference among Apo E2, E3, and E4 is caused by mutations at two amino acid residues. The most common variant, Apo E3, is characterized by a cysteine at residue 112 and an arginine at residue 158. The Apo E2 variant has a cysteine at both residues 112 and 158, whereas the Apo E4 variant has an arginine at both residues 112 and 158. These differences change the structure of the Apo E protein which results in differential binding affinity, protein stability and domain interactions, ultimately leading to altered lipoprotein metabolism and potentially disease predispositions as well as differential responses to dietary and

lifestyle management.

Disease association

A recent meta-analyses of studies of Apo E genotypes with TC (total cholesterol), LDL, HDL or triglycerides (involving data on up to 86,067 participants in 82 studies) and with CHD (coronary heart disease, involving data on up to 37,850 cases and 82,727 controls in121 studies) confirms many previous observations that in healthy human populations, the effect of Apo E shows a significant stepwise increase as a function of genotype (E2/E2, to E3/E2, to E4/E2, to E3/E3, to E4/E3, to E4/E4). There are approximately linear relationships of Apo E genotypes with both LDL-C (LDL cholesterol) levels and CHD risk (Fig. 1). Compared with individuals with the E3/E3 genotype, E2 carriers have a 20% lower risk of CHD and E4 carriers have a slightly higher risk. HDL and triglycerides concentration was not affected by Apo E genotypes (Bennet et al, 2007).

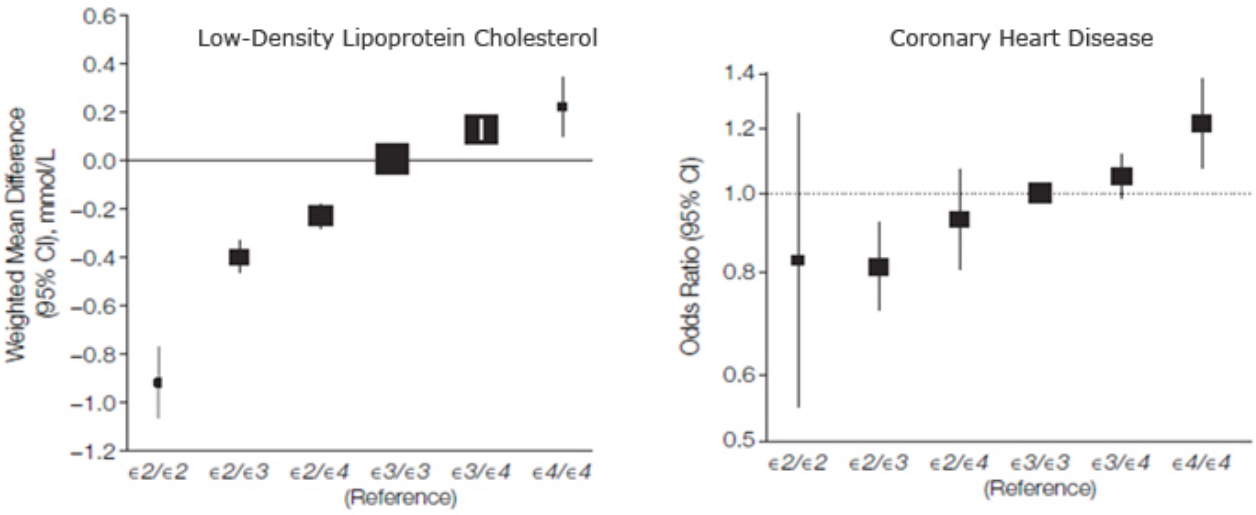

Figure 1. LDL cholesterol levels (left) and odds ratio by for CHD as a function of Apolipoprotein E genotypes in studies with 1,000 or more healthy individuals, using people with the E3/E3 genotype as the reference group (Adapted from Bennet et al, 2007).

Although E2 carriers has low level of LDL and low risk of CHD, an association between Apo E2/2 and type III hyperlipoproteinemia, a disease first described by Addison and Gull in 1851, has been known for decades. Type III hyperlipoproteinemia is also known as dysbetalipoproteinemia, familial dysbetalipoproteinemia, broad beta disease, and remnant removal disease. This disorder is characterized by increased blood chylomicrons remnants and IDL (intermediate density lipoprotein) levels and premature vascular disease, including both CHD and peripheral artery disease. Affected individuals may develop multiple yellowish, lipid-filled bumps or plaques on the skin and buildup of fatty materials in the blood vessels (arthrosclerosis) that potentially obstruct blood flow, causing coronary heart disease or peripheral vascular disease. It is noteworthy to point out that Apo E2/2 genotype contributes to the type III hyperlipoproteinemia phenotype being a necessary, not a sufficient factor. For example, a recent report shows that the ApoC3 3238 G>C and ApoA5 -1131 T>C polymorphism may exacerbate the hyperlipidemic phenotype of type III hyperlipoproteinemia patients (Henneman et al, 2009). This also explains the association of type III hyperlipoproteinaemia with diabetes and hypothyroidism. Overproduction of apo B or VLDL are other secondary factors that precipitate overt type III HLP in the hypolipidemic apoE2 mice, and this has also been suggested in humans. In addition, the expression level of Apo E2 seems to play an important role. For example, LDL null mice are hypolipidemic when Apo E2 is low (&ls; 10mg/ml) and hyperlipidemic when ApoE2 is high (> 10mg/ml) (Mahley et al, 1999).

Apo E4 allele is associated with late-onset sporadic Alzheimer's disease in a variety of ethnic groups. Alzheimer's disease (AD) is characterized by the accumulation and deposition of Aβ peptides within the brain, leading to the perturbation of synaptic function and neuronal loss that typifies the disease. Although 40 to 65% of AD patients have at least one copy of the E4 allele, Apo E4 is not a determinant of the disease - at

least a third of patients with AD are Apo E4 negative and some Apo E4 homozygotes never develop the disease. Yet those with two E4 alleles have up to 20 times the risk of developing AD (Corder et al, 1993).

Dietary response

Diet is the major reason for variation in serum cholesterol concentration in human population. The ability of dietary intervention to improve plasma lipoprotein-lipid profiles varies greatly among individuals with different Apo E genotypes. Ordovas reports in a comprehensive review of 27 studies that focused on the Apo E genotype and dietary response (Ordovas, 1999). In general, the E4 allele appears to be the most responsive to a low-fat and low-cholesterol dietary intervention; however, they may not be the most responsive to changes in other aspects of the diet. For example, subjects carrying the E2 allele had the greatest change in total and LDL cholesterol in response to wheat- or oat-bran supplementation. Tea drinking and possibly a fruit and vegetable diet have more favorable response on plasma lipid levels in subjects carrying the Apo E2 allele. A long-term increase in dietary soluble fiber does not affect fat metabolism after meals in subjects with the Apo E4 allele; however, it does enhance fat absorption in Apo E3/3 subjects. A detailed listing of the studies and results from the original publication are summarized in Table 3 (Ordovas, 1999).

Exercise response

Physical exercise reduces total and LDL cholesterol while increasing HDL cholesterol level in general. The first evidence that plasma lipoprotein-lipid responses to exercise training might be influenced by the Apo E genotype was published in 1996 (Taimela, 1996). The leisure-time physical activity levels and lipoprotein-lipid profiles of 1,500 Finnish children and young adults aged 9 to 24 years were accessed. In conclusion, no correlation was found in females. However, in Apo E3/4 and E3/3 men, there was an inverse effect of physical activity level on plasma total cholesterol and LDL cholesterol and a positive effect on HDL cholesterol/total cholesterol ratio, and in Apo E2/3 men there were even stronger relationships between physical activity levels and these factors. In contrast, in Apo E4/4 men physical activity levels did not affect plasma lipoprotein-lipid levels. Another study on the correlation of CV (cardiovascular) fitness and Apo E genotypes concludes that the overall plasma lipoprotein-lipid profiles of Apo E3 men and women appear to be affected more by increased CV fitness than those of Apo E2 and Apo E4 men and women (St. Amand et al, 1999). A recent longitudinal intervention study assessing the impact of Apo E genotype on plasma lipoprotein-lipid responses to exercise training found that middle-aged and older Apo E2 genotype men had larger overall plasma lipoprotein-lipid profile improvements with prolonged endurance exercise training than otherwise comparable Apo E3 and Apo E4 genotype men (Hagberg et al, 1999).

The overall conclusion is that exercise training does not affect plasma lipoprotein-lipid levels in Apo E4 individuals, has a moderate effect in Apo E3 individuals, and has an even greater effect in Apo E2 individuals (Table 4).

Table 4. Plasma lipoprotein-lipid changes with exercise training as a function of Apo E genotype.

	E2	E3	E4
Total Cholesterol	-7	-12	0
LDL Cholesterol	-11	-9	-2
HDL Cholesterol	8	3	2
Triglycerides	-32	-23	1

All values are expressed in units of mg/dl and are means ± SE (adopted from Hagberg et al, 2000. Physiol Genomics 4: 101–108).

Cholesterol-lowering medication response

Hagberg et al (2000) reviewed twelve studies that investigated the association between polymorphic Apo E variation and plasma lipoprotein-lipid changes with lipid-lowering medications. Nine of these studies used

statins (which target HMG-CoA reductase) as the intervention, two used probucol (which targets CETP), three used gemfibrozil (which targets PPARα), and one used cholestyramine (which blocks the absorption of bile salt). The general conclusions are that Apo E2 genotype individuals respond more favorably in terms of plasma total and LDL cholesterol than Apo E3 carriers, which respond more favorably than Apo E4 individuals to statins, gemfibrozil, and possibly cholestyramine therapy; while Apo E4 individuals respond more favorably in terms of plasma lipoprotein-lipid profiles than Apo E3 homozygous individuals to probucol therapy. For the response to statins, some evidence indicates that this interaction may be sex specific, with the interaction being more evident in men.

Hormone replacement therapy effect

Premenopausal women carrying Apo E2 and E3 genotype appear to improve plasma lipoprotein-lipid profiles more favorably with hormone replacement therapy than Apo E4 carrying women. With 5 years of continuous estrogen and cyclic progestin therapy, only women with Apo E2 or E3 alleles decreased plasma total (8.1%) and LDL cholesterol levels (17.1%) and increased plasma HDL cholesterol levels (13.1%) whereas no plasma total, LDL, or HDL cholesterol changes were evident in women with at least one Apo E4 allele.

Molecular mechanisms

Structural difference among Apo E2, E3 and E4 proteins leads to variations in binding affinity, protein stability, and protein domain-to-domain interaction. Ultimately, these variations are reflected in the function of the Apo E protein: lipoprotein metabolism.

As illustrated in Figure 2, in a normal E3/E3 genotype (middle panel), food digestion in the gut leads to formation of chylomicrons, which are degraded by a series of lipoprotein lipase in blood circulation to give rise to chylomicron remnants, which are taken up by LPR receptors into the liver cells. The liver cells then synthesize VLDL lipoproteins and release them into the circulation. VLDL is degraded by lipoprotein lipase in blood circulation to give rise to VLDL remnants, also known as IDL. IDL can either be taken up by the liver cells via the LPR or the LDL receptor pathway, or it can be further degraded by lipoprotein lipase to LDL, which in turn is taken up by the LDL-receptor pathway or the non-receptor route. When lipoprotein concentration is too high, extra chylomicron and VLDL can also be cleared by bile salt in liver.

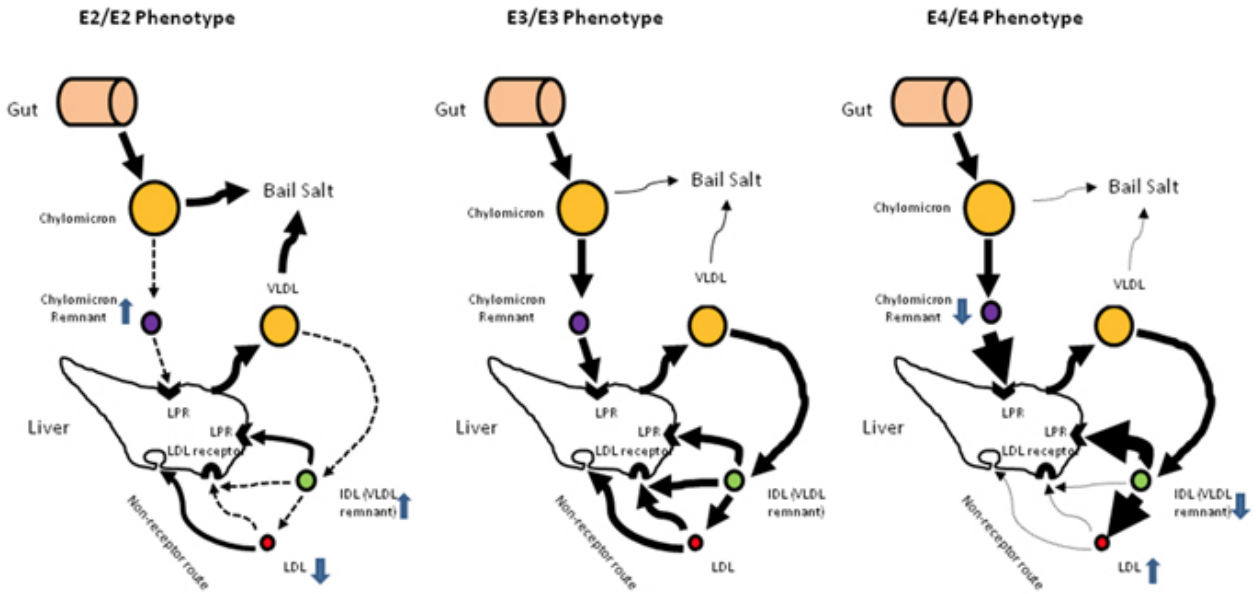

Figure 2. Chylomicron, VLDL and LDL metabolism in three Apo E phenotypes. The weight of the solid black arrows is meant to be proportional to the rate of conversion. The dashed arrows indicate impaired steps. The grey arrows indicate concentration changes of a particular lipoprotein. All the changes are compared to the E3/E3 phenotype, which is assumed to reflect normal metabolism.

In the E2/E2 genotype (left panel in Fig. 2), the LDL-receptor binding and the lipoprotein lipase degradation of chylomicron, VLDL, and IDL are impaired. Therefore, overall lipoprotein metabolism rate is slowed down. The phenotypes manifest in elevated chylomicron and IDL and decreased LDL, thus lower LDL cholesterol and lower coronary heart disease risk. In contrast, in E4/E4 genotype (right panel in Fig. 2), the LDL-receptor binding and the lipoprotein lipase degradation of chylomicron, VLDL, and IDL are enhanced. Therefore, the overall lipoprotein metabolism rate is increased. The phenotypes manifest in decreased chylomicron and IDL and elevated LDL, thus higher LDL cholesterol and coronary heart disease risk.

The phenotypes of a single E2 or E4 carriers are more or less in between E2/E2 and E4/E4. The phenotype of E2/E3 is between that of E2/E2 and E3/E3; E4/E3 is between that of E4/E4 and E3/E3; E2/E4 is close to E3/E3 with a little lining toward E3/E4 side.

With the above molecular mechanism in mind, specific questions are addressed in the following sections.

Why does Apo E2 genotype show a cholesterol-lowering effect?

Despite the invariable presence of b-VLDL (chylomicrons remnants and IDL), most E2/E2 subjects are either normolipidemic or even hypocholesterolemic. Historically, the defective binding of Apo E2-containing lipoproteins to the LDL receptors was assumed to be responsible for the LDL cholesterol-lowering effect of Apo E2. It was hypothesized that either the defective binding of Apo E2 or the poor competition between defective Apo E2-containing remnants and apoB 100-containing LDL to the LDL receptor results in the up-regulation of the LDL receptor expression, thus a faster clearance of LDL, leading to enhanced clearance of the LDL. These hypotheses were later disapproved by the transgenic mouse studies reported by the Gladstone Institute of Cardiovascular Disease (Mahley et al, 1999). The LDL cholesterol-lowering effect of Apo E2 in wild type and LDL receptor null mice are indistinguishable. Later, *in vitro* and *in vivo* studies using transgenic mice with various genetic backgrounds suggest that Apo E2 inhibits the lipolytic activity of LPL (lipoprotein lipase), leading to decreased LDL formation and lower LDL cholesterol in circulation.

How does Apo E2 inhibit LPL activity?

The Apo E protein in the plasma of the Apo E2/E2 genotype is 51 to 276% more compared to Apo E3/E3 genotype (Siest et al, 1995), probably due to the relatively more stable protein structure of Apo E2 than Apo E3. A higher concentration of Apo E2 in the blood may displace Apo C-II, a well-defined cofactor for LPL, leading to the inhibition of LPL activity, thus the impairment of chylomicron and VLDL lipolysis, thus less conversion of chylomicron remnants and IDL to LDL. In the transgenic mouse studies, significantly decreased apo C-II content in the remnants of the apo E2 mice was observed. Non-transgenic VLDL contained 19 mg of mouse apo E and 32 mg of apo C-II per mg of triglycerides. In contrast, the VLDL from the LDL receptor-null mice expressing apoE2 contained an abundance of apoE2 (51 mg) but only 5 mg of apo C-II (Mahley et al, 1999).

Why does the Apo E2/E2 genotype show hypolipidemic mostly but associate with hyperlipidemic in type III hyperlipoproteinaemia cases?

One feature of the Apo E2/E2 genotype, regardless of the cholesterol level, is the higher concentration of triglycerides in the plasma. The high level of triglycerides is the result of impaired LPL activity, which results in a slow rate of lipoprotein clearance. In a normal person, the slightly higher triglycerides do not impose a major threat. When the diet, lifestyle, medication or genetic background are changed in a way that could increase remnant lipoprotein production and overwhelm the clearance pathway, in combination with the defective receptor binding of Apo E2, the remnant accumulation and hyperlipidemia would occur. For example, transgenic mice studies show that crossing the hypolipidemic apoE2 with mice over expressing human apo B converted the hypolipidemic phenotype of the apo E2 mice to a hyperlipidemic phenotype characterized by a pronounced accumulation of remnants and decreased LDL cholesterol (Mahley et al, 1999), consistent with implications in humans (Hazzard et al, 1981).

Why does the Apo E4 genotype show a cholesterol-increasing effect?

Apo E4 increases plasma LDL levels thanks to its preferential binding to VLDL and remnants, which may accelerate their clearance, leading to down-regulation of LDL receptors and increased LDL levels. Alternatively, remnants could compete for LDL receptors, retarding LDL clearance.

What role does Apo E play in the pathology of Alzheimer's disease?

It is widely believed that amyloid beta (Aβ) deposits are the fundamental cause of Alzheimer's disease. The brain possesses robust intrinsic Aβ clearance mechanisms. Aβ peptides are degraded within the brain principally by neprilysin (NEP) and insulin degrading enzyme (IDE, insulysin). In the central nervous system, Apo E is synthesized by astrocytes, activated microglia, and neurons. It binds to Aβ and influences the deposition or clearance of Aβ. Studies with APP transgenic mice have demonstrated Apo E isoform-specific effects on the propensity of Aβ to be deposited in the brain (E4 > E3 > E2) (Holtzman, 2004). These effects might be due to the ability of Apo E in promoting the proteolysis of Aβ peptides by NEP and IDE within microglia. Importantly, the ApoE4 isoform, which is associated with increased risk for AD, exhibits an impaired ability to promote Aβ proteolysis compared to the Apo E2 and Apo E3 isoforms (Jiang et al, 2008).

How do Apo E genotypes impact response to dietary cholesterol?

Several mechanisms have been proposed to explain the Apo E genotype differences in individual response to dietary therapy. For example, the rate of LDL clearance is slow in E2 and faster in E4 when compared to E3 (Weintraub et al, 1987). Some studies have shown that intestinal cholesterol absorption is related to Apo E phenotypes. When the response of an E3/3 phenotype was used for comparison, individuals with an E3/2 phenotype had a lower rate of intestinal absorption of cholesterol, while those with an E4/3 phenotype had a higher rate (Divignon et al, 1988). Other mechanisms, such as different distribution of Apo E on the lipoprotein fractions, LDL-apo B production, bile acid and cholesterol synthesis and postprandial lipoprotein clearance, may also be involved.

How do Apo E genotypes impact cholesterol response to physical exercise?

Physical exercise has been widely adopted as a practice to reduce the "bad cholesterol" LDL and increase the "good cholesterol" HDL. Cholesterol is not an energy source. So exactly how physical exercise improves the cholesterol profile is not well understood.

Researchers now believe there are several mechanisms involved. First, exercise stimulates enzymes that help move LDL from the blood to the liver, probably through the remnant receptor pathway. From there, the cholesterol is converted into bile for digestion or excreted. So the more you exercise, the more LDL your body expels. Second, exercise increases lipoprotein lipase activity which in turn accelerates the breakdown of triglycerides, resulting in a transfer of cholesterol and other substances to the HDL (Grandjean et al, 2000).

In Apo E2 genotypes, the LDL receptor pathway is defective and the lipolysis of chylomicrons and VLDL is slowed down due to impaired lipoprotein lipase activity in the Apo E2-containing particles. These defects force the remnant receptor pathway to become the major Apo E2-containing lipoprotein clearance route. In response to physical exercise, the remnant receptor route is strengthened, therefore the clearance of remnants is enforced and the conversion to LDL is further reduced. The slow conversion of chylomicron and VLDL to LDL in Apo E2 also stimulates the transfer of cholesterol from those particles to HDL. In Apo E4 genotypes, the LDL receptor pathway is dominant and physical exercise can only divert a proportion of Apo E4-containing lipoprotein particles through the remnant pathway. In addition, the concentration of chylomicron and VLDL are much lower due to the faster clearance rate from Apo E4, resulting in less transfer of cholesterol from these lipoproteins to HDL. Therefore, the cholesterol profile response in Apo E2 genotype is more favorable than Apo E4, with Apo E3 being the normal genotype in the middle.

How do Apo E genotypes impact statin medication response?

Statins are HMG-CoA reductase inhibitors that reduce plasma cholesterol levels by inhibiting this rate-limiting enzyme in cholesterol biosynthesis. This inhibition increases the hepatic production of LDL receptors, thus increasing hepatic LDL uptake and reducing plasma LDL cholesterol levels. Individuals carrying the Apo E4 allele tend to have lipoproteins with an enhanced binding capacity to the LDL receptor. This enhanced binding increases the removal rate of these lipoproteins by hepatocytes, increasing the intracellular concentration of cholesterol in the liver and causing a down-regulation in the production of HMG-CoA reductase and LDL receptors. On the other hand, lipoproteins containing Apo E2 have a reduced binding affinity for the LDL receptor; thus their plasma clearance rate is reduced. This lowers intracellular cholesterol levels and up-regulates HMG-CoA reductase synthesis. Consequently, it is reasonable to expect that HMG-CoA reductase inhibitors would be less effective in reducing cholesterol levels in APO E4 individuals, as they may already have relatively low-HMG-CoA reductase activities.

Why does the Apo E2/E2 genotype induced type III HLP show gender difference?

Among Apo E2/E2 genotypes, men can develop the hyperlipidemia after adolescence, whereas women almost never develop the disorder until after menopause. It was hypothesized that these gender-dependent phenotypes were caused by estrogen activity in women. Using transgenic apo E2 rabbit model, researchers at the Gladstone Institute of Cardiovascular Disease proved this hypothesis by showing that estrogen treatment prevents the male apo E2 rabbit from developing the hyperlipidemia while ovariectomy of female apoE2 transgenic rabbits would induce it (Huang et al, 1997). It is therefore speculated that estrogen modulates lipid levels in the context of the apoE2 allele by altering both receptor expression and lipolytic activity (Mahley et al, 1999).

Do infectious diseases drive Apo E evolution?

The source of differences in the Apo e allele frequencies among population groups is unknown. Apo E3 is the most common, but Apo E4 may be the ancestral allele. Many animals, including all the great apes, have an apo E4-like allele (Arg-112) and do not display multiple isoforms. It is unlikely that the detrimental effects of apo E4 in cardiovascular or neurological disease provided the evolutionary pressure, as these effects are post-reproductive. Any genetic drift from apo E4 to apo E3 to apo E2 most likely results from the selective pressures of infectious diseases (Mahley et al, 2009). Two examples are under discussion, for which the evidence must be considered as preliminary. In hepatitis C infections, apoE4 carriers incurred less fibrotic damage by allele dose, whereas Brazilian slum children carrying apoE4 showed fewer diarrheas and associated impairments of cognitive development (Finch, 2010).

Conclusions

Diet, exercise, disease association and medication responses have been studied extensively on each of the six Apo E genotypes. Specific diet regimens have been designed for each to optimize the potential impact of nutrition on decreasing risks associated with the APOE gene. Personalized cholesterol management plans are waiting for you to explore at GB HealthWatch.

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