Apolipoprotein E and Its Association with Alzheimer’s Disease

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Apolipoprotein E (apo E) has long been recognized as a determinant of coronary artery disease risk. Recently though, it has also been noted for its potential pathogenic role in Alzheimer’s disease (AD). The gene for apo E is polymorphic in the population. The three common alleles are e2, e3, and e4 and they code for specific forms of apo E differing by a single amino acid substitution. Among middle aged Caucasians, 78% have the e3 allele, 15% have at least one e4 allele and 7% are at least heterozygous for the e2 allele1. Over ninety separate studies indicate that the e4 allele confers an increased risk of developing AD. The 2% of the Caucasian population who end up being homozygous for the e4 allele (e4/e4) are also at an eight times greater risk of developing AD than those without AD. This may suggest that most of the selection pressure due to the e4 allele is attributable to mortality from AD as opposed to coronary artery disease5.

Therefore to begin to understand apo e4’s relationship to Alzheimer’s disease and premature mortality, selective survival plays an important role in the epidemiology of apo E genotypes. Since certain genotypes are associated with premature mortality, either from atherosclerosis or AD, those subjects with such deleterious genotypes tend to die off with age, leaving behind a cohort with the remaining, less mortality-related genotypes1. The e4 allele has indeed been found to be such a selective factor. The allelic frequency of e4 markedly declines with age among older subjects to the point that in two studies of centenarians, the allelic frequency was between two and five percent1. The allelic frequency of e4 also falls with age when observing two groups: normal controls and subjects with AD. As one can see in Figure 1, the decline (or drop out) in e4 frequency is much steeper among AD subjects than among those without AD. This may suggest that most of the selection pressure due to the e4 allele is attributable to mortality from AD as opposed to coronary artery disease6.

![Figure 1: The allelic frequency of e4 falls with age when observing two groups: normal controls and subjects with AD. The decline (or drop out) in e4 frequency is much steeper among AD subjects than among those without AD. This may suggest that most of the selection pressure due to the e4 allele is attributable to mortality from AD as opposed to coronary artery disease.](image-url)
we must also have a good understanding of this protein’s role in atherosclerosis as well. Apo E is an integral part of various lipoproteins including chylomicron remnants, VLDL, IDL and HDL. As such, it facilitates the binding of these lipoproteins to receptor sites (the LDL receptor and the chylomicron remnant receptor) found on hepatocytes and other tissue cells.

Chylomicron remnant particle uptake by the liver is facilitated by the apolipoprotein E which is found within the chylomicron remnant. Because Apo E also binds to the LDL receptor, it also facilitates binding of IDL and HDL to hepatocytes. The liver, in turn, is responsible for the conversion of IDL to LDL and transporting the cholesterol associated with HDL to bile (see Figure 2).

The human Apo E gene is 3.7 kb long, contains four exons and is located on chromosome 19. Genes for apolipoprotein C (I, I' and II) occur in the same area. Of particular note is the fact that the low density lipoprotein (LDL) receptor is also located on chromosome 19.

Several cholesterol-related syndromes have been related to specific Apo E genotypes. The majority of patients with type III hyperlipidemia are homozygous for the Apo E-e2 allele. These patients have decreased clearance of VLDL and chylomicron remnants from the circulation because apo E-2 binds to hepatic LDL and chylomicron remnant receptors abnormally. It is important to note that only 1% of those homozygous for apo E-2 actually express this disease and thus, an additional defect which attenuates the patient’s ability to compensate for the binding defect must also be occurring. Clinically, 80% of patients have palmar or tuberous xanthomas (typically on the knees or elbows) and premature coronary heart disease. Lipoprotein electrophoresis reveals a broad beta band (type 3 pattern) that indicates elevated amounts of chylomicron remnants and IDL.

Regarding Apo e4’s potentiation of atherosclerosis, this protein actually enhances VLDL conversion to LDL, thus decreasing VLDL levels and increasing LDL levels in the circulation. Because of increased circulat-

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**Figure 2:** This cartoon depicts the various roles apolipoprotein E plays in fat metabolism. Chylomicron remnant particle uptake by the liver is facilitated by the apolipoprotein E which is found within the chylomicron remnant. Because Apo E also binds to the LDL receptor, it also facilitates binding of IDL and HDL to hepatocytes.
ing LDL, among the three major apo E alleles, the e4 allele is associated with the greatest risk for coronary artery disease.

Given all that we know about apo e4 and its atherogenic tendencies, it would be nice if we could somehow tie this information to a potential pathogenic role in AD. In fact, there may indeed be a connection. AD is characterized neuropathologically by senile plaques rich in a small peptide abnormally cleaved from the amyloid precursor protein. This peptide is called, BA4. Apo E has been found to bind tightly to p-A4 in vitro. In addition, apo E has been noted within senile plaques by immunoreactive staining. The gross amount of B-amyloid deposition in the cortex is also found to be higher in those having at least one e4 allele compared to those without e4 and the density of cortical plaques in AD patients is highest among those with the e4/e4 genotype, then the e3/e4 followed by the e3/e3 genotype. Apo e4 has also been noted to be capable of interacting with tau protein in such a way that might lead to neurofibrillary tangle formation, another neuropathological hallmark of AD.

Another mechanism by which apo E may be involved in the pathogenesis of AD, is apo E's interaction with LDL receptor-related protein (LRP). LRP is a protein found in the central nervous system on the membrane surfaces of neurons and astrocytes. LRP has been postulated to be a scavanger of, BA4-apo E complexes. Once LRP binds to the, BA4-apo E complexes, they are internalized by the astrocyte and degraded within lysosomes. One hypothesis for why apo E4 predisposes for AD is that this isoform interacts with BA4 and/or the LRP in such away that effective scavenging is inhibited (see Figure 3).

Despite the important association between the Apo E-e4 allele and Alzheimer's disease, other risk factors must play important roles. Essentially, the apo E 4 gene has been found to be neither necessary nor sufficient for the development of AD. Reasons include: Studies have noted a small number (4%) of older subjects without AD who are nonetheless homozygous for the e4 allele. If the e4 allele was the only necessary "event" to produce AD, then the risk of developing AD for e4 homozygotes should be 100%.

- The association between certain genotypes and AD may vary according to race. A Manhattan, New York study did note similar e4 allele risk ratios (for AD) for African-Americans Hispanics and Whites. However, among African Americans, the e2/e3 genotype conferred an eightfold increased risk for AD, whereas this same genotype among whites appeared to be protective against AD.

- Some studies have shown discordance between monozygotic twins in the development of AD, thus implicating the role of non-genetic accomplies.

So, given what we know about apo E thus far, what can we gain from Apo E genotyping? There may be at least two useful situations. 1. To use apo E genotype as a "qualitative " predictor for AD among those with mild cognitive impairment. In a study of patients presenting with mild cognitive impairment (scoring 1.5 times the standard deviation below age-appropriate norms for various tests), apo E genotype was a useful predictor for future rate of cognitive decline. The rate of progression to Alzheimer's disease was greatest for those homozygous for the e4 allele. As a tool in differential diagnosis. At least among Caucasians, if a person presents with cognitive impairment and they have at least one e2 allele, the clinician would be swayed to look for causes other than AD. Again as noted by Maestre and colleagues, this would not be the case for an African-American patient.

What we know about apo E so far would indicate that there is certainly more to the pathogenesis of AD than this particular apolipoprotein, and in particular, the e 4 allele. The ethnic variation in risk for AD according to apo E genotype especially indicates the possibility of other genes that play important roles (either protective or predisposing) which may be tightly linked to the apo E locus. Monozygotic twin discordance in the expression of AD also suggests the importance of environmental factor(s) playing a role in the pathogenesis of AD. Therefore, apo E genotyping is currently not a dependable tool for assessing an individual's risk of developing AD.
Figure 3: This cartoon depicts hypothetically the potential roles apolipoprotein E might play in the pathogenesis of Alzheimer's Disease. AD is characterized neuropathologically by senile plaques (SP) rich, BA4 protein. Apo E has also been noted within senile plaques and it binds tightly to BA4 protein. Apo E also interacts with LDL receptor-related protein (LRP). LRP is a protein found in the central nervous system on the membrane surfaces of neurons and astrocytes. LRP has been postulated to be a scavenger of, BA4-apo E complexes. Once LRP binds to the, B-A4-apo E complexes, they are internalized by the astrocyte and degraded within lysosomes. One hypothesis for why apo E4 predisposes for AD is that this isoform interacts with, B-A4 and/or the LRP in such a way that effective scavenging is inhibited (see Figure 3).

References:


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