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GENE MUTATIONS IN APOE, Aβ, PRESINILIN GENES AND ALZHMEIRS DISEASE

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ABSTRACT

Alzheimer disease (AD) is a genetically complex disorder. Mutations in genes ApoE, Presenilin 1 & 2 and amyloid precursor protein may be implicated in the pathogenesis of the disease. In this review, we discuss current advances in AD genetics, implications of the known AD genes, on the clinical diagnosis, treatment and genetic counseling of patients and families with early- and late-onset AD.

KEYWORDS: Alzheimer Disease; ApoE, Presenilin 1 & 2 and Amyloid Precursor Protein.

INTRODUCTION

Alzheimer's disease (AD), the most common progressive neurodegenerative disease results from irreversible loss of neurons, particularly in the cortex and hippocampus. A major focus of AD research has been to understand the genetic etiology of AD and its relationship to AD neuropathology. The key neuropathological features of AD are abundant neurofibrillary tangles composed of hyperphosphorylated tau protein and senile plaques made of β-amyloid (Aβ). Over 2 decades of genetic research has resulted in a better understanding of the pathway leading to the accumulation of insoluble protein, Aβ. The accumulation of Aβ is considered a central component in the pathogenesis of AD and has been associated with the 3 autosomal dominant, deterministic genes known to be involved in Early Onset Alzhmeirs Disease (EOAD), Presenilin 1 (PSEN1), Presenilin 2 (PSEN2), and Amyloid Precursor Protein (APP). A fourth gene,

apolipoprotein E (APOE), has been confirmed as a susceptibility factor/risk factor for late onset AD (LOAD). As our understanding of the genes involved in the disease evolves, so may the ability to identify at- risk individuals who would be eligible for early treatment and prevention.

Genes and Alzheimer's disease

AD is a progressive neurodegenerative disorder characterized by a gradual destruction of brain cells that results in a progressive decline in mental functions (e.g., memory or ability to learn, reason, make judgments, and communicate), culminating in severe dementia. At advanced stages, this decline leaves the patient unable to carry out daily activities, such as dressing, eating, or personal hygiene. Moreover, the patient's personality and behavior may change so that he or she becomes more anxious, agitated, suspicious, or even aggressive.

Alzheimer's disease (AD) is neuropathologically characterized by extracellular senile plaques containing amyloid beta (Aβ) and intracellular neurofibrillary tangles containing hyperphosphorylated tau protein. Mendelian forms of the disease are caused by mutations in the amyloid precursor protein (APP) gene and the presenilin 1 and 2 genes (PSEN1 and PSEN2 respectively). While only apolipoprotein E (APOE) has been clearly identified as a susceptibility gene in the more common form of AD, data from recent genome-wide association studies has implicated several other common risk variants.[1-8] Intracellular neurofibrillary lesions composed of the microtubule-associated protein tau and extracellular amyloid plaques assembled from the Aβ peptide are the pathological hallmarks that characterize Alzeheimer's disease. Unlike amyloid plaques, the spatial and temporal appearance of tau lesions correlates closely with the progression of disease. Therefore, identifying the underlying mechanisms of tau lesion formation is of critical importance for understanding the disease. Mutations in the MAPT gene encoding tau protein lead to neurofibrillary lesions, neurodegeneration, and cognitive decline. Although it depends on the location within the coding sequence, most tau missense mutations have been shown to increase aggregation propensity. In Alzheimer's disease, tau protein associated with neurofibrillary lesions is mostly found to be hyperphosphorylated. Hyperphosphorylation of tau acts to increase the free tau concentration available for aggregation. Postmortem histopathological examination of amyloid plaques and neurofibrillary tangles in the brain is still the only method to

definitively confirm the diagnosis of AD. Because tau can serve as a surrogate marker for neurodegeneration in AD, detection of tau aggregates is of practical importance for disease.

The AD have two forms: the rare early onset Alzheimer's disease, where first symptoms appear before the age of 65; and the much more common late onset Alzheimer's disease, where typically the first symptoms develop after this age. These two types of Alzheimer's disease generally have different patterns of genetic inheritance.

Early onset Alzheimer's disease

This form of Alzheimer's tends to cluster within families, sometimes with several generations affected, in which case it is called familial disease. In some of these cases, early onset Alzheimer's is caused by mutations in one of three genes. These three genes are the amyloid precursor protein gene (APP) and two presenilin genes (PSEN-1 and PSEN-2). People with any of these extremely rare mutations tend to develop Alzheimer's disease in their 30s or 40s.

Amyloid Precursor Protein

The amyloid precursor protein gene (APP, OMIM 104,760, chromosome 21q21) encodes a ubiquitously expressed, integral Type I membrane glycoprotein that exists as different alternatively spliced isoforms, with three predominant ones: APP751, APP770, and APP695, the latter being the main isoform found in the brain.[9] The proteolytic processing of APP results in the production of different peptides (including Aβ), after a series of secretase cleavages, and occurs through two mutually exclusive pathways: the amyloidogenic pathway (fundamentally considered as the pathogenic pathway) and the non-amyloidogenic or constitutive pathway.[10-12] The identification of Aβ as a metabolic product of APP and the reports of AD families harboring APP causative mutations led to the general concept that Aβ is a key player in the development of AD, and that EOAD mutations are influencing the properties or ratios of the different Aβ isoforms in the brain.[13] Dominant mutations in APP are, however, a rare cause of AD with an estimated frequency of 16% of familial EOAD patients.[14] More recently, two mutations in APP (A673V and E693Δ) have been reported to cause AD only in the homozygous state in families with apparently recessive modes of inheritance.[15,16]

Presenilin 1 & 2

The presenilin 1 (PSEN1, OMIM 104,311, chromosome 14q24.3) and presenilin 2 (PSEN2, OMIM 600,759, chromosome 1q31-q42) genes have a very similar genetic structure and encode two proteins expressed in a multiplicity of tissues including the brain, with higher levels in the cerebellum and the hippocampus and a primarily neuronal expression.[17, 18] These are highly homologous, sharing an overall amino acid sequence identity of 67%. Hydrophobicity plots predicted these to be integral membrane proteins[18] most likely adopting a transmembrane structure containing nine segments with a hydrophilic intracellular loop region.[19,20] PSENs are important components of the multimeric gamma-secretase complex and are predominantly located in the endoplasmic reticulum and Golgi compartments, clearly suggesting their involvement in protein processing.[21,22] The first disease causing mutations in PSEN1 and PSEN2 were identified in 1995.[18,23] Today, 175 pathogenic mutations and seven variants nonpathogenic or with unclear pathogenicity have been identified in PSEN1. PSEN2 harbors fewer mutations: 14 pathogenic mutations and nine variants nonpathogenic or with unclear pathogenicity. The PSENs mutation range encompasses mainly missense mutations scattered all over the proteins, with some clustering around transmembrane domains.[24, 25]

Late onset Alzheimer's disease

A small but growing number of genes have now been identified which affect - to different degrees – the chances of developing late onset Alzheimer's. The effects of these genes are subtle, with variations acting to increase or decrease the risk of developing Alzheimer's disease, but not directly to cause it. The gene with the greatest known influence on the risk of developing late onset Alzheimer's disease is called apolipoprotein E [APOE). This gene is found on chromosome 19 and comes in three forms, which by convention are named with the Greek letter epsilon (ε): APOE ε2, APOE ε3 and APOE ε4. All individuals have two copies of the APOE gene, and these may be the same as each other or different. Hence each have one of the six possible combinations are possible: ε2/ε2, ε2/ε3, ε3/ε3, ε2/ε4, ε3/ε4 or ε4/ε4. APOE ε4 is associated with a higher risk of Alzheimer's. About a quarter of the general population inherits one copy of the APOE ε4 gene. This increases their lifetime risk of developing Alzheimer's disease by up to four times. About 2 per cent of the population gets a 'double dose' of the APOE ε4 gene - one from each parent. This increases their risk of developing Alzheimer's disease by about 10

times or more. However, even then, they are not certain to develop Alzheimer's. About 60 per cent of the population has a 'double dose' of the APOE ε3 gene and is at 'average' risk. Up to half of this group develops Alzheimer's disease by their late 80s. The APOE ε2 form of the gene is mildly protective against Alzheimer's: people with it are slightly less likely to develop the disease. In the general population, 11 per cent has one copy of APOE ε2 together with a copy of APOE ε3, and one in 200 (0.5 per cent) has two copies of APOE ε2. Recent scientific developments have allowed researchers to test many more genes to see whether there are additional links with Alzheimer's disease. This approach has revealed further genes which are linked to increased risk, called CLU, PICALM, CR1, BIN1, ABCA7, MS4A, CD33, EPHA1 and CD2AP. Variants in these genes are linked to significant differences in risk of Alzheimer's, but their effects are much smaller than for APOE.

ApoE

Circulating ApoE is synthesized mainly in liver and it is associated to lipoproteins, but astrocytes and possibly microglia are important sources for apoE in brain.[26, 27] ApoE has an important function as a regulator of lipid metabolism during development and is involved in the growth and regeneration of injured neurons.[28] The levels of apoE increase after brain lesions[29, 30] which may contribute to the regeneration of neurons.

The mechanisms by which the ε4 allele convey the development of AD are largely unclear but many studies have revealed isoform specific effects on neurodegeneration, formation of NFTs and β-amyloid. Arendt et al.[31] have shown that plastic responses in brain are impaired in ε4 carriers, and in vitro studies have shown that apoE3 promotes neurite outgrowth more than apoε4.[32] ApoE ε4 carriers have also more severe astrogliosis compared to ε4 non-carriers.[33]

Accumulating data suggest that apoE plays a role in the development of neurofibrillary and amyloid pathology. ApoE3 has been shown to bind avidly to microtubule-associated proteins[34] and to promote their polymerization, and apoE4 is claimed to depolymerize microtubules.[35] The stabilizing effect of apoE3 may prevent the abnormal phosphorylation of the tau protein.[36] In addition to the in vitro data, neuropathological studies have shown that the apoE ε4 allele is linked to increased density of NFTs in brain.[37, 38] On the other hand, ApoE is bound strongly to β-amyloid plaques.[39] In vitro studies have indicated that apoE4 promotes β-amyloid aggregation[40 – 42], and apoE3

inhibits the aggregation of β-amyloid.[43] The accumulation of β-amyloid in brain is increased in controls and AD patients carrying the ε4 allele.[44 – 46] This effect may be based on the augmentation of Aβ40 deposition.[47, 48] In contrast, AD patients carrying the ε2 allele have a decreased amyloid burden.[49] It has also been suggested that the apoE ε4 allele increases vascular β-amyloid deposition.[50] and amyloid accumulation after a traumatic brain injury.[51]

Clinical studies support the significance of apoE in the development of AD. MRI studies have shown that AD patients with at least one ε4 allele have decreased volume in their entorhinal cortex.[52] and hippocampus.[53] In single photon emission computed tomography (SPECT), AD patients homozygous for ε4 allele exhibit the most severe cerebral hypoperfusion[54], and in positron emission tomography (PET) the low baseline metabolism in non-demented ε4 carriers predicts a cognitive decline.[55] In neuropsychological tests, the ε4 allele has been associated with the cognitive decline in subjects with cognitive impairment, but not in cognitively normal individuals.[56]

Despite the strong association between AD and apoE ε4 allele, apoE genotyping is not recommended in the routine diagnosis of AD. The presence of the ε4 allele by itself does not confirm AD, and the disease cannot be excluded if an individual does not carry the risk allele.

In the population based study of Hyman et al.[57] over half of the individuals over 80 years of age carrying two ε4 alleles were cognitively normal. Therefore, apoE genotyping provides only a marginal increase in the confidence of the diagnosis and cannot be used as a diagnostic test for AD.[58]

Diagnosis of Alzheimer disease

The clinical diagnosis of AD, based on signs of slowly progressive dementia and findings of gross cerebral cortical atrophy on neuroimaging, is correct about 80 –90% of the time. The association of the APOE e4 allele with AD is significant; however, APOE genotyping is neither fully specific nor sensitive. APOE genotyping may have an adjunct role in the diagnosis of AD in symptomatic individuals and a limited role at this time in predictive testing of asymptomatic individuals. Three forms of EOAD caused by mutations in one of three genes (APP, PSEN1, and PSEN2) are recognized. The APP is cleaved by alpha- and gamma-secretases to form the Aβ peptide, which is the primary

component of the extracellular amyloid plaque deposited in AD. Presenilin 1 (PS1) is part of the gamma-secretase complex (and PS2 is a close homolog of PS1). Molecular genetic testing of the three genes is available in clinical laboratories.

Establishing the diagnosis of Alzheimer disease relies on clinical-neuropathologic assessment.[59] Neuropathologic findings on autopsy examination remain the gold standard for diagnosis of AD. The clinical diagnosis of AD (before autopsy confirmation) is correct about 80–90% of the time.[60]

- Clinical signs: slowly progressive dementia,
- Neuroimaging: gross cerebral cortical atrophy[61], fb
- Neuropathologic findings: microscopic extracellular amyloid-β (Aβ) neuritic plaques, intraneuronal neurofibrillary tangles, and amyloid angiopathy at postmortem examination. The plaques should stain positively with Aβ-amyloid antibodies and negative for prion antibodies, which are diagnostic of prion diseases. The numbers of plaques and tangles must exceed those found in age-matched controls without dementia. Aggregation of alpha-synuclein in the form of Lewy bodies may also be found in neurons in the amygdale.[62]

Treatment

Treatment is supportive. Each symptom is managed on an individual basis. Assisted living arrangements or care in a nursing home is usually necessary. Drugs that increase cholinergic activity by inhibiting acetylcholinesterase produce a modest but useful behavioral or cognitive benefit in some affected individuals. Antidepressant medication may improve associated depression. The first such drug was tacrine; however, this agent is also hepatotoxic. Newer such drugs with similar pharmacologic action, such as Aricept® (donepezil)[63–65], Exelon® (rivastigmine)[66] and galantamine,[67–69] are not hepatotoxic.

Vitamins and other over-the-counter medications have been used in the treatment of AD.[70] Some, but not all, reports suggest that affected individuals taking 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A reductase inhibitors for hypercholesteralemia have a reduced incidence of dementia.[71-73] Immunization of an AD mouse model with β-amyloid has attenuated the AD pathology and stimulated the search for a possible vaccination approach to the treatment of human AD.[74] A human trial of this approach was halted because of encephalitis in a few subjects.[75-77] Alternative approaches to immunization

therapy have been proposed.[78] Thus far, treatment of symptomatic AD with estrogens has not proven beneficial.[79, 80]

Perspectives

There have been huge advances in our understanding of the genetics of AD over the last few years. The discovery of the three EOAD-related genes, APP, PSEN1, and PSEN2, has improved our knowledge of the physiopathology of AD. Ongoing and future large-scale genome-wide association studies and next-generation whole genome or whole exome sequencing hold the promise of unraveling the complexities of the genetic architecture of this disease. This should lead to identification of novel targets for genetic testing, as well as developing preventative and curative therapies for AD.

REFRENCES

1. Beecham GW, Martin ER, Li YJ, Slifer MA, Gilbert JR, et al. Genomewide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. Am J Hum Genet., 2009; 84: 35–43.
2. Bertram L, Lange C, Mullin K, Parkinson M, Hsiao M, et al. Genomewide association analysis reveals putative Alzheimer's disease susceptibility loci in addition to APOE. Am J Hum Genet., 2008; 83: 623– 632.
3. Carrasquillo MM, Zou F, Pankratz VS, Wilcox SL, Ma L, et al. Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease. Nat Genet., 2009; 41: 192–198.
4. Coon KD, Myers AJ, Craig DW, Webster JA, Pearson JV, et al. A highdensity whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. J Clin Psychiatry., 2007; 68: 613–618.
5. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet., 2009; 41: 1088–1093.
6. Jun G, Naj AC, Beecham GW, Wang LS, Buros J, et al. Meta-analysis Confirms CR1, CLU, and PICALM as Alzheimer Disease Risk Loci and Reveals Interactions With APOE Genotypes. Arch Neurol., 2010.
7. Lambert JC, Heath S, Even G, Campion D, Sleegers K, et al. Genomewide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet, 2009; 41: 1094–1099.

8. Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. Jama., 2010; 303: 1832–1840.
9. Yoshikai, S., Sasaki, H., Doh-Ura, K., Furuya, H., Sakaki, Y. Genomic organization of the human amyloid beta-protein precursor gene. Gene., 1990; 87: 257–263.
10. Esch, F.S., Keim, P.S., Beattie, E.C., Blacher, R.W., Culwell, A.R., Oltersdorf, T., McClure, D., Ward, P.J. Cleavage of amyloid beta peptide during constitutive processing of its precursor. Science., 1990; 248: 1122–1124.
11. Haass, C., Schlossmacher, M.G., Hung, A.Y., Vigo-Pelfrey, C., Mellon, A., Ostaszewski, B.L., Lieberburg, I., Koo, E.H., Schenk, D., Teplow, D.B. Amyloid beta-peptide is produced by cultured cells during normal metabolism. Nature., 1992; 359: 322–325.
12. Shoji, M., Golde, T.E., Ghiso, J., Cheung, T.T., Estus, S., Shaffer, L.M., Cai, X.D., McKay, D.M., Tintner, R., Frangione, B., Production of the Alzheimer amyloid beta protein by normal proteolytic processing. Science., 1992; 258: 126–129.
13. Hardy, J. Amyloid, the presenilins and Alzheimer's disease. Trends Neurosci., 1997; 20: 154–159.
14. Raux, G., Guyant-Marechal, L., Martin, C., Bou, J., Penet, C., Brice, A., Hannequin, D., Frebourg, T., Campion, D. Molecular diagnosis of autosomal dominant early onset Alzheimer's disease: an update. J Med Genet, 2005; 42: 793–795.
15. Di Fede, G., Catania, M., Morbin, M., Rossi, G., Suardi, S., Mazzoleni, G., Merlin, M., Giovagnoli, A.R., Prioni, S., Erbetta, A., Falcone, C., Gobbi, M., Colombo, L., Bastone, A., Beeg, M., Manzoni, C., Francescucci, B., Spagnoli, A., Cantu, L., Del Favero, E., Levy, E., Salmona, M., Tagliavini, F. A recessive mutation in the APP gene with dominant-negative effect on amyloidogenesis. Science., 2009; 323: 1473–1477.
16. Tomiyama, T., Nagata, T., Shimada, H., Teraoka, R., Fukushima, A., Kanemitsu, H., Takuma, H., Kuwano, R., Imagawa, M., Ataka, S., Wada, Y., Yoshioka, E., Nishizaki, T., Watanabe, Y., Mori, H., 2008. A new amyloid beta variant favoring oligomerization in Alzheimer'stype dementia. Ann Neurol., 2008; 63: 377–387.
17. Levy-Lahad, E., Poorkaj, P., Wang, K., Fu, Y.H., Oshima, J., Mulligan, J., Schellenberg, G.D. Genomic structure and expression of STM2, the chromosome 1 familial Alzheimer disease gene. Genomics., 1996; 34: 198–204.
18. Rogaev, E.I., Sherrington, R., Rogaeva, E.A., Levesque, G., Ikeda, M., Liang, Y., Chi, H., Lin, C., Holman, K., Tsuda, T. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3

gene. Nature., 1995; 376: 775–778.

19. Henricson, A., Kall, L., Sonnhammer, E. L. A novel transmembrane topology of presenilin based on reconciling experimental and computational evidence. FEBS J, 2005; 272: 2727–2733.
20. Laudon, H., Hansson, E.M., Melen, K., Bergman, A., Farmery, M.R., Winblad, B., Lendahl, U., von Heijne, G., Naslund, J. A ninetransmembrane domain topology for presenilin 1. J. Biol Chem., 2005; 280: 35352–35360.
21. Kovacs, D.M., Fausett, H.J., Page, K.J., Kim, T.W., Moir, R.D., Merriam, D.E., Hollister, R.D., Hallmark, O.G., Mancini, R., Felsenstein, K.M., Hyman, B.T., Tanzi, R.E., Wasco, W. Alzheimer-associated presenilins one and 2: neuronal expression in brain and localization to intracellular membranes in mammalian cells. Nat Med., 1996; 2: 224–229.
22. De Strooper, B. Aph-one, Pen-two, and Nicastrin with Presenilin generate an active gamma-Secretase complex. Neuron., 2003; 38: 9–12.
23. Sherrington, R., Rogaev, E.I., Liang, Y., Rogaeva, E.A., Levesque, G., Ikeda, M., Chi, H., Lin, C., Li, G., Holman, K. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature., 1995; 375: 754–760.
24. Guerreiro, R.J., Baquero, M., Blesa, R., Boada, M., Bras, J.M., Bullido, M.J., Calado, A., Crook, R., Ferreira, C., Frank, A., Gomez-Isla, T., Hernandez, I., Lleo, A., Machado, A., Martinez-Lage, P., Masdeu, J., Molina-Porcel, L., Molinuevo, J.L., Pastor, P., Perez-Tur, J., Relvas, R., Oliveira, C.R., Ribeiro, M.H., Rogaeva, E., Sa, A., Samaranch, L., Sanchez-Valle, R., Santana, I., Tarraga, L., Valdivieso, F., Singleton, A., Hardy, J., Clarimon, J. Genetic screening of Alzheimer's disease genes in Iberian and African samples yields novel mutations in presenilins and APP. Neurobiol Aging., 2010; 31(5): 725–731.
25. Hardy, J., Crook, R., 2001. Presenilin mutations line up along transmembrane alpha-helices. Neurosci Lett., 2001; 306: 203–205.
26. Pitas RE, Boyles JK, Lee SH, Foss D and Mahley RW. Astrocytes synthesize apolipoprotein E and metabolize apolipoprotein E-containing lipoproteins. Biochim Biophys Acta., 1987; 917: 148-161.
27. Nakai M, Kawamata T, Taniguchi T, Maeda K and Tanaka C. Expression of apolipoprotein E mRNA in rat microglia. Neurosci Lett., 1996; 211: 41-44.
28. Poirier J. Apolipoprotein E in animal models of CNS injury and in Alzheimer's disease. Trends Neurosci., 1994; 17: 525-530.

29. Poirier J, Hess M, May PC and Finch CE. Astrocytic apolipoprotein E mRNA and GFAP mRNA in hippocampus after entorhinal cortex lesioning. Brain Res Mol Brain Res., 1991; 11: 97-106.
30. Page KJ, Hollister RD and Hyman BT. Dissociation of apolipoprotein and apolipoprotein receptor response to lesion in the rat brain: an in situ hybridization study. Neuroscience., 1998; 85: 1161-1171.
31. Arendt T, Schindler C, Bruckner MK, Eschrich K, Bigl V, Zedlick D and Marcova L. Plastic neuronal remodeling is impaired in patients with Alzheimer's disease carrying apolipoprotein epsilon 4 allele. J Neurosci., 1997; 17: 516-529.
32. Nathan BP, Bellosta S, Sanan DA, Weisgraber KH, Mahley RW and Pitas RE. Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. Science 1994; 264: 850-852.
33. Overmyer M, Helisalmi S, Soininen H, Laakso M, Riekkinen P, Sr. and Alafuzoff I. Astrogliosis and the ApoE genotype. an immunohistochemical study of postmortem human brain tissue. Dement Geriatr Cogn Disord., 1999; 10: 252-257.
34. Huang DY, Goedert M, Jakes R, Weisgraber KH, Garner CC, Saunders AM, Pericak-Vance MA, Schmechel DE, Roses AD and Strittmatter WJ. Isoform-specific interactions of apolipoprotein E with the microtubule-associated protein MAP2c: implications for Alzheimer's disease. Neurosci Lett., 1994; 182: 55-58.
35. Nathan BP, Chang KC, Bellosta S, Brisch E, Ge N, Mahley RW and Pitas RE. The inhibitory effect of apolipoprotein E4 on neurite outgrowth is associated with microtubule depolymerization. J Biol Chem., 1995; 270: 19791-19799.
36. Strittmatter WJ, Weisgraber KH, Goedert M, Saunders AM, Huang D, Corder EH, Dong LM, Jakes R, Alberts MJ, Gilbert JR and et al. Hypothesis: microtubule instability and paired helical filament formation in the Alzheimer disease brain are related to apolipoprotein E genotype. Exp Neurol., 1994; 125: 163-171; discussion 172-164.
37. Nagy Z, Esiri MM, Jobst KA, Johnston C, Litchfield S, Sim E and Smith AD. Influence of the apolipoprotein E genotype on amyloid deposition and neurofibrillary tangle formation in Alzheimer's disease. Neuroscience., 1995; 69: 757-761.
38. Ohm TG, Kirca M, Bohl J, Scharnagl H, Gross W and Marz W. Apolipoprotein E polymorphism influences not only cerebral senile plaque load but also Alzheimer-type neurofibrillary tangle formation. Neuroscience., 1995; 66: 583-587.
39. Namba Y, Tomonaga M, Kawasaki H, Otomo E and Ikeda K. Apolipoprotein E immunoreactivity in cerebral amyloid deposits and neurofibrillary tangles in Alzheimer's

disease and kuru plaque amyloid in Creutzfeldt-Jakob disease. Brain Res., 1991; 541: 163-166.

40. Ma J, Yee A, Brewer HB, Jr., Das S and Potter H. Amyloid-associated proteins alpha 1-antichymotrypsin and apolipoprotein E promote assembly of Alzheimer b-protein into filaments. Nature., 1994; 372: 92-94.
41. Sanan DA, Weisgraber KH, Russell SJ, Mahley RW, Huang D, Saunders A, Schmechel D, Wisniewski T, Frangione B, Roses AD and et al. Apolipoprotein E associates with b amyloid peptide of Alzheimer's disease to form novel monofibrils. Isoform apoE4 associates more efficiently than apoE3. J Clin Invest., 1994; 94: 860-869.
42. Wisniewski T, Castano EM, Golabek A, Vogel T and Frangione B. Acceleration of Alzheimer's fibril formation by apolipoprotein E in vitro. Am J Pathol., 1994; 145: 1030-1035.
43. Evans KC, Berger EP, Cho CG, Weisgraber KH and Lansbury PT, Jr. Apolipoprotein E is a kinetic but not a thermodynamic inhibitor of amyloid formation: implications for the pathogenesis and treatment of Alzheimer disease. Proc Natl Acad Sci USA., 1995; 92: 763-767.
44. Rebeck GW, Reiter JS, Strickland DK and Hyman BT. Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions. Neuron., 1993; 11: 575-580.
45. Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, Pericak-Vance MA, Goldgaber D and Roses AD. Increased amyloid b-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. Proc Natl Acad Sci USA 1993;90:9649-9653.
46. Gomez-Isla T, West HL, Rebeck GW, Harr SD, Growdon JH, Locascio JJ, Perls TT, Lipsitz LA and Hyman BT. Clinical and pathological correlates of apolipoprotein E epsilon 4 in Alzheimer's disease. Ann Neurol., 1996b; 39: 62-70.
47. Gearing M, Mori H and Mirra SS. Ab-peptide length and apolipoprotein E genotype in Alzheimer's disease. Ann Neurol., 1996; 39: 395-399.
48. Ishii K, Tamaoka A, Mizusawa H, Shoji S, Ohtake T, Fraser PE, Takahashi H, Tsuji S, Gearing M, Mizutani T, Yamada S, Kato M, St. George-Hyslop PH, Mirra SS and Mori H. Ab1-40 but not Ab1-42 levels in cortex correlate with apolipoprotein E epsilon4 allele dosage in sporadic Alzheimer's disease. Brain Res., 1997; 748: 250-252.
49. Polvikoski T, Sulkava R, Haltia M, Kainulainen K, Vuorio A, Verkkoniemi A, Niinistö L, Halonen P and Kontula K. Apolipoprotein E, dementia, and cortical

deposition of b-amyloid protein. N Engl J Med., 1995; 333: 1242-1247.

50. Zarow C, Zaias B, Lyness SA and Chui H. Cerebral amyloid angiopathy in Alzheimer disease is associated with apolipoprotein E4 and cortical neuron loss. Alzheimer Dis Assoc Disord., 1999; 13: 1-8.
51. Nicoll JA, Roberts GW and Graham DI. Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid β-protein following head injury. Nat Med., 1995; 1: 135-137.
52. Juottonen K, Lehtovirta M, Helisalmi S, Riekkinen PJ, Sr. and Soininen H. Major decrease in the volume of the entorhinal cortex in patients with Alzheimer's disease carrying the apolipoprotein E epsilon4 allele. J Neurol Neurosurg Psychiatry., 1998; 65: 322-327.
53. Lehtovirta M, Soininen H, Laakso MP, Partanen K, Helisalmi S, Mannermaa A, Ryynanen M, Kuikka J, Hartikainen P and Riekkinen PJ, Sr. SPECT and MRI analysis in Alzheimer's disease: relation to apolipoprotein E epsilon 4 allele. J Neurol Neurosurg Psychiatry., 1996; 60: 644-649.
54. Lehtovirta M, Kuikka J, Helisalmi S, Hartikainen P, Mannermaa A, Ryynanen M, Riekkinen P and Soininen H. Longitudinal SPECT study in Alzheimer's disease: relation to apolipoprotein E polymorphism. J Neurol Neurosurg Psychiatry., 1998; 64: 742-746.
55. Small GW, Ercoli LM, Silverman DH, Huang SC, Komo S, Bookheimer SY, Lavretsky H, Miller K, Siddarth P, Rasgon NL, Mazziotta JC, Saxena S, Wu HM, Mega MS, Cummings JL, Saunders AM, Pericak-Vance MA, Roses AD, Barrio JR and Phelps ME. Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. Proc Natl Acad Sci USA., 2000; 97: 6037-6042.
56. Dik MG, Jonker C, Bouter LM, Geerlings MI, van Kamp GJ and Deeg DJ. APOE-epsilon4 is associated with memory decline in cognitively impaired elderly. Neurology 2000; 54: 1492-1497.
57. Hyman BT, Gomez-Isla T, Briggs M, Chung H, Nichols S, Kohout F and Wallace R. Apolipoprotein E and cognitive change in an elderly population. Ann Neurol., 1996; 40: 55-66.
58. Mayeux R, Tang MX, Jacobs DM, Manly J, Bell K, Merchant C, Small SA, Stern Y, Wisniewski HM and Mehta PD. Plasma amyloid b-peptide 1-42 and incipient Alzheimer's disease. Ann Neurol., 1999; 46: 412-416.
59. Bird TD, Miller BL. Alzheimer's disease and primary dementias. In: Kasper D, Fauci A, Branwald E, Longo DL, et al., editors. Harrison's principles of internal medicine, 16th ed.

New York: McGraw-Hill, 2005; 2393–2406.

60. Mayeux R, Saunders AM, Shea S, Mirra S, et al. Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. N Engl J Med., 1998; 338: 506 –511.
61. Kaye JA. Diagnostic challenges in dementia. Neurology., 1998; 51: 45–52.
62. Popescu A, Lippa CF, Lee VM, Trojanowski JQ. Lewy bodies in the amygdala: increase of alpha-synuclein aggregates in neurodegenerative diseases with taubased inclusions. Arch Neurol., 2004; 61: 1915–1919.
63. Feldman H, Gauthier S, Hecker J, Vellas B, et al. Economic evaluation of donepezil in moderate to severe Alzheimer disease. Neurology., 2004; 63: 644–650.
64. Seltzer B, Zolnouni P, Nunez M, Goldman R, et al. Efficacy of donepezil in earlystage Alzheimer disease: a randomized placebo-controlled trial. Arch Neurol., 2004; 61: 1852–1856.
65. Petersen RC, Thomas RG, Grundman M, Bennett D, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med., 2005; 352: 2379–2388.
66. 66. Rogers SL, Friedhoff LT. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial. The Donepezil Study Group. Dementia., 1996; 7: 293–303.
67. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology., 2000; 54: 2261–2268.
68. Tariot PN, Solomon PR, Morris JC, Kershaw P, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology., 2000; 54: 2269 –2276.
69. Mega MS, Dinov ID, Porter V, Chow G, et al. Metabolic patterns associated with the clinical response to galantamine therapy: a fludeoxyglucose f 18 positron emission tomographic study. Arch Neurol., 2005; 62: 721–728.
70. 70. Yaffe K, Clemons TE, McBee WL, Lindblad AS. Impact of antioxidants, zinc, and copper on cognition in the elderly: a randomized, controlled trial. Neurology., 2004; 63: 1705–1707.
71. Wolozin B, Kellman W, Ruosseau P, Celesia GG, et al. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol., 2000; 57: 1439 –1443.
72. Li G, Higdon R, Kukull WA, Peskind E, et al. Statin therapy and risk of dementia in

the elderly: a community-based prospective cohort study. Neurology., 2004; 63: 1624–1628.

73. Li G, Larson EB, Sonnen JA, Shofer JB, et al. Statin therapy is associated with reduced neuropathologic changes of Alzheimer disease. Neurology., 2007; 69: 878–885.
74. Schenk D, Barbour R, Dunn W, Gordon G, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature., 1999; 400: 173–177.
75. Check E. Nerve inflammation halts trial for Alzheimer drug. Nature., 2002; 415: 462.
76. Ferrer I, Boada Rovira M, Sanchez Guerra ML, Rey MJ, et al. Neuropathology and pathogenesis of encephalitis following amyloid-beta immunization in Alzheimer's disease. Brain Pathol., 2004; 14: 11–20.
77. Gilman S, Koller M, Black RS, Jenkins L, et al., AN1792(QS-21)-201 Study Team. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology., 2005; 64: 1553– 1562.
78. Qu B, Boyer PJ, Johnston SA, Hynan LS, et al. Abeta42 gene vaccination reduces brain amyloid plaque burden in transgenic mice. J Neurol Sci., 2006; 244: 151–158.
79. Mulnard RA, Cotman CW, Kawas C, van Dyck CH, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA., 2000; 283: 1007–1015.
80. Wang PN, Liao SQ, Liu RS, Liu CY, et al. Effects of estrogen on cognition, mood, and cerebral blood flow in AD: a controlled study. Neurology., 2000; 54: 2061–2066.