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Genetics of Alzheimer Disease

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Abstract

Alzheimer disease (AD) is the most common causes of neurodegenerative disorder in the elderly individuals. Clinically, patients initially present with short-term memory loss, subsequently followed by executive dysfunction, confusion, agitation, and behavioral disturbances. Three causative genes have been associated with autosomal dominant familial AD (*APP*, *PSEN1*, and *PSEN2*) and 1 genetic risk factor (*APOE*ε4 allele). Identification of these genes has led to a number of animal models that have been useful to study the pathogenesis underlying AD. In this article, we provide an overview of the clinical and genetic features of AD.

Keywords

Alzheimer disease; genetics; neurodegeneration

Introduction

Prevalence and Incidence

Alzheimer disease ([AD] OMIM #104300) is the most common irreversible, progressive cause of dementia. It is characterized by a gradual loss of memory and cognitive skills. Alzheimer disease accounts for over 50% of all dementia cases, and it presently affects more than 24 million people worldwide. Moreover, over 5 million new cases of AD are reported each year, and the incidence increases from 1% between the ages of 60 and 70 to 6% to 8% at the age of 85 years or older[1] and is likely to increase as a greater proportion of the population ages.2

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The prevalence and incidence of AD strongly suggest that age is the most influential known risk factor. Indeed, AD prevalence increases significantly with age, and AD incidence increases from 2.8 per 1000 person years for people between 65 and 69 years to 56.1 per 1000 person years for people who are older than 90 years.[3] Approximately 10% of persons older than 70 years have significant memory loss, and more than half of these individuals have probable AD. An estimated 25% to 45% of persons older than 85 years have dementia.[4] The duration of disease is typically 8 to 10 years, with a range from 2 to 25 years after diagnosis.

The disease is divided into 2 subtypes based on the age of onset: early-onset AD (EOAD) and late-onset AD (LOAD). Early-onset AD accounts for approximately 1% to 6% of all cases and ranges roughly from 30 years to 60 or 65 years. However, LOAD, which is the most common form of AD, is defined as AD with an age at onset later than 60 or 65 years. Both EOAD and LOAD may occur in people with a positive family history of AD. Approximately 60% of EOAD cases have multiple cases of AD within their families, and of these familial EOAD cases, 13% are inherited in an autosomal dominant manner with at least 3 generations affected.[5,6] Early-onset disease can also occur in families with late-onset disease.[4] With the exception of a few autosomal dominant families that are single-gene disorders (see below), most AD cases appear to be a complex disorder that is likely to involve multiple susceptibility genes and environmental factors.[4,7–10] Although the first-degree relatives of patients with late-onset disease have approximately twice the expected lifetime risk of the disease, the pattern of transmission is rarely consistent with Mendelian inheritance.

Clinical Symptoms

Both EOAD and LOAD present clinically as dementia that begins with a gradual decline of memory and then slowly increases in severity until the symptoms eventually become incapacitating. An inability to retain recently acquired information is typically the initial presentation, whereas memory for remote events is relatively spared until later. With disease progression, impairment in other areas of cognition (eg, language, abstract reasoning, and executive function or decision making) occurs to varying degrees and typically is associated with difficulty at work or in social situations or household activities. Changes in mood and affect often accompany the decline in memory. Delusions and hallucinations are not typically presenting signs but can present any time during the course of illness. Neurological symptoms that may occur later in the course of illness include seizures, hypertonia, myoclonus, incontinence, and mutism. Death commonly occurs from general inanition, malnutrition, and pneumonia.[4] Treatment of AD with cholinesterase inhibitors and memantine may result in slowing of cognitive decline in patients with mild-to-moderate dementia, but current treatments do not modify the course of illness.[11,12]

Clinical Diagnosis

Currently, the diagnosis of AD is based on clinical history, neurological examination, and neuropsychological tests. The *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition [*DSM-IV*]) criteria for diagnosing dementia requires the loss of 2 or more of the following: memory, language, calculation, orientation, or judgment.[13] Another commonly used criteria, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Work Group requires the presence of dementia that is documented by clinical examination, deficits in at least 2 cognitive domains, absence of other systemic disorders, progressive worsening of memory for the diagnosis of "probable AD."[14]

The Mini-Mental State Examination (MMSE) is 1 bedside test that can help to evaluate changes in a patient's cognitive abilities. In addition, a diagnosis of probable AD necessitates the exclusion of other neurodegenerative disorders associated with dementia, such as frontotemporal dementia (including frontotemporal dementia with parkinsonism 17 and Pick disease), Parkinson disease, diffuse Lewy body disease, Creutzfeldt-Jakob disease, and cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy (CADASIL).[15] Discriminating AD from other forms of dementia is usually done through clinical history and neurological examination.4 In addition, other systemic causes of dementia need to be excluded, especially the treatable forms of cognitive impairment, such as impairment due to depression, chronic drug intoxication, chronic central nervous system infection, thyroid disease, vitamin deficiencies (eg, B_{12} and thiamine), central nervous system angitis, and normal-pressure hydrocephalus.[4]

Neuropathological Diagnosis

A definitive diagnosis of AD requires a clinical assessment of probable AD as well as postmortem confirmation, with the presence of 2 histopathological features: neurofibrillary tangles and amyloid plaques.[16–18] Expert clinicians correctly diagnose AD, 80% to 90% of the time.[19] Even though plaques and tangles are often found in cognitively normal age-matched controls, the density of the plaques and the distribution of neurofibrillary tangles are more severe in patients with AD, according to standardized histological assessments.[16] According to a consensus work group, the following categories are recommended to provide an estimate of the likelihood that AD pathological changes underlie dementia:

1. There is a high likelihood that dementia is due to AD lesions when the postmortem brain shows the presence of both neuritic plaques and neurofibrillary tangles in neocortex (ie, a frequent neuritic plaque score according to CERAD [Consortium to Establish a Registry for Alzheimer's Disease [20] and a stage V/VI according to Braak and Braak.21
2. There is an intermediate likelihood that dementia is due to AD lesions when the postmortem brain shows moderate neocortical neuritic plaques and neurofibrillary tangles in limbic regions (ie, CERAD moderate and Braak and Braak stage III/IV).
3. There is a low likelihood that dementia is due to AD lesions when the postmortem brain shows neuritic plaques and neurofibrillary tangles in a more limited distribution and/or severity (ie, CERAD infrequent and Braak and Braak stage I/II). [22] The precise pathogenic mechanisms that are responsible for the development of these changes remain unknown.

The major component of amyloid plaques, found in AD brain, is amyloid-β (Aβ).23,24 The most common form of Aβ in humans is 40 amino acids long and is called Aβ40. A 42-amino-acid–long fragment, Aβ42, is less abundant than Aβ40 and differs only in that it has 2 additional amino acid residues at the C-terminus. The Aβ42 fragment is associated with AD. 25 Amyloid-β is derived from the amyloid precursor protein (APP) after cleavage by secretases. First, α-secretase (nonneurotoxic "normal" cleavage) or β-secretase (potential neurotoxic "abnormal" cleavage) cleaves APP, and a second cleavage of the β-secretase product, by γ-secretase, cleaves APP further to produce Aβ26–32 (Figure 1). Depending on the point of cleavage by γ-secretase, 2 main forms of Aβ are produced consisting of either 40 or 42 amino acid residues (Aβ40 or Aβ42). The proportion of Aβ40 to Aβ42 that is formed is particularly important in AD because Aβ42 is far more prone to oligomerize and form fibrils than the more abundantly produced Aβ40 peptide. Indeed, although it appears that the production of Aβ isoforms is a normal process of unknown function, in a small number of individuals, an increased proportion of Aβ42 appears sufficient to cause EOAD.[18,33]

Neurons bearing neurofibrillary tangles are another frequent finding in AD brains,[34,35] and the temporal and spatial appearance of these tangles, which contain hyperphosphorylated tau, more closely reflects disease severity than does the presence of amyloid plaques.[36,37] Tangles are formed by hyperphosphorylation of a microtubule-associated protein known as tau, causing it to aggregate in an insoluble form. However, neurofibrillary tangles are also found in other disorders, such as frontotemporal dementia and progressive supranuclear palsy. Moreover, these tangles are not necessarily associated with the cognitive dysfunction and memory impairment that is typical of AD and mutations in the gene that encodes the tau protein (*MAPT*), a main component of neurofibrillary tangles, have not been genetically linked to AD.[24]

Genetics of AD

Introduction

Overall, more than 90% of patients with AD appear to be sporadic and to have a later age at onset of 60 to 65 years of age (LOAD).[38] Although twin studies support the existence of a genetic component in LOAD, no causative gene has been yet identified. Indeed, the only gene that has been consistently found to be associated with sporadic LOAD, across multiple genetic studies, is the apolipoprotein E (*APOE*) gene[39–43] (Table 1). However, many carriers of the *APOE* risk allele (ε4) live into their 90s, which suggests the existence of other LOAD genetic and/or environmental risk factors that have yet to be identified. To this end, several unreplicated genetic variants have been reported, and these findings suggest that there may be 5 to 7 major LOAD susceptibility genes.[4,44,45] For a catalog of candidate gene association studies, please refer to the AlzGene online database (http://www.alzforum.org/res/com/gen/alzgene/default.asp).

Genes Associated With Autosomal Dominant AD

Although several hundred families carry one of the following mutations, they account for less than 1% of cases.

AD1: Amyloid precursor protein (APP)

Inheritance and clinical features: In the 1980s, Kang and colleagues purified both plaque and vascular amyloid deposits and isolated their 40-residue constituent peptide (Aβ), which subsequently led to the cloning of the APP type I integral membrane glycoprotein from which Aβ is proteolytically derived.[46] The *APP* gene was then mapped to chromosome 21q, which accounted for the observation that patients with Down syndrome (trisomy 21) develop amyloid deposits and the neuropathological features of AD when in their 40s.[24,47–49]

Since then, over 32 different *APP* missense mutations have been identified in 85 families. Interestingly, most of these mutations are located at the secretase cleavage sites or the *APP* transmembrane domain on exons 16 and 17 (Figure 2). Information regarding *APP* mutations are available in the NCBI database and the Alzheimer Disease Mutation Database (www.molgen.ua.ac.be/ADMutations).[50] Mutations within *APP* account for 10% to15% of early-onset familial AD (EOFAD),[4,51–53] appear to be family specific, and do not occur within the majority of sporadic cases with AD. The majority of these EOFAD mutations are in or adjacent to the Aβ peptide sequence (Figure 2), the major component of amyloid plaques [54,55] Most cases[56] containing *APP* mutations have an age of onset in the mid-40s and -50s.

Gene location and structure: Sequences encoding *APP* were first cloned by screening complementary DNA (cDNA) libraries.[46] The initial full-length cDNA clone encoded a

695-amino-acid protein (APP695)40 and consisted of 18 exons. The *APP* gene, located on chromosome 21q21, is alternatively spliced into several products, named according to their length in amino acids (ie, APP695, APP714, APP751, APP770, and APP563) and expressed differentially by tissue type, whereby the 3 isoforms that are most relevant to AD are restricted to the central nervous system (APP695) or expressed in both the peripheral and central nervous system (CNS) tissues (APP751 and APP770).[46,57–63]

Gene function and expression: Amyloid precursor protein is a type-I integral-membrane protein46 that resembles a signal-transduction receptor. It is expressed in many tissues and concentrated in the synapses of neurons. Its primary function is not known, though it has been implicated in neural plasticity64 and as a regulator of synapse formation.[65] Amyloid precursor protein is synthesized in the endoplasmic reticulum, posttranscriptionally modified in the Golgi (N- and O-linked glycosylation, sulfation, and phosphorylation), and transported to the cell surface via the secretory pathway. Amyloid precursor protein is also endocytosed from the cell surface and processed in the endosomal–lysosomal pathway.[66,67] Amyloid precursor protein and its by-product Aβ have been found to be translocated inside mitochondria and implicated in mitochondrial dysfunction.[68–70]

Proteolysis of APP by α-secretase or β-secretase leads to the secretion of soluble fragment amyloid-α peptide (sAPPα) or soluble fragment amyloid-β peptide (sAPPβ). This proteolysis generates C-terminal fragments of 10 and 12 kDa, respectively, which are inserted into the membrane. These fragments can be cut by γ-secretase to extracellularly release the Aβ peptide71 and intracellularly release a cytoplasmic fragment identified as amyloid precursor protein intracellular domain72 ([AICD] see Figure 1). The majority of EOFAD mutations alter this processing of *APP* in such a way that Aβ42 levels are changed relative to other Aβ isoform levels.[73,74] The function of these *APP* proteolytic fragments is still unclear.

The missense *APP* “Swedish” mutations (*APP*SW, *APP*K670N, and M671L) and the “London” mutations (*APP*LON and *APP*V717I) are examples of *APP* mutations that lead to increased Aβ production and development of AD.[75,76] Transgenic mouse models of such *APP* mutations (PDAPP, Tg2576, APP23, TgCRND8, and J20) have been developed.[77] Each of these mouse models have different APP expression levels and different neurorological abnormalities.[77,78] For example, the Tg2576 mouse model that carries the “Swedish” mutation has high*APP*levels, highAβ levels, and cognitive disturbances[79] that are progressive and start as early as 6 months of age.[80]

Genetic variation: Amyloid precursor protein transcripts have been identified in which exons 7, 8, and 15 are alternatively spliced. APP695, the predominant isoform in neurons,[81] contains exon 15 but excludes exons 7 and 8. The APP751 and APP770 isoforms both encode Kunitz-type protease inhibitor (KPI)-containing forms of APP,[58–60,82] are present in both peripheral tissue and neurons, and contain exons 16 and 17 but exclude exons 7, 8, and 15. The gene region that encodes the portion of APP that is cleaved to produce the Aβ peptide is located within exons 16 and 17 of the APP770 splice variant83 (see Figure 2). Other splice variants have been observed, with missing exon 15 in various combinations with exons 7 and 8; these splice variants are referred to as L-APPs.[82,84] A number of studies have indicated that alternative splicing of exons 7 and 8 is modulated in brain during aging and possibly during AD.[84–89] Even though the function of APP and its various splice variants is unknown, differential expression of these splice variants between tissues may imply functional differences. It is important to note that although most of the described splice variants contain Aβ-encoding sequences, 2 additional rare transcripts, APP365 and APP563, do not, implicating additional functionally important variability in APP isoform function.[62,90]

The first described and best characterized *APP* mutation (V717I) is located within the transmembrane domain near the γ-secretase cleavage site[75] (Figure 2). Other substitutions have since been identified at this site, and several groups have reported the V717I mutation in families who are unrelated to the initial London family. Many other *APP* mutations have since been identified, especially near the γ-secretase cleavage site, and the bulk of these mutations have been associated with modulation of Aβ levels. For example, a C-terminal L723P mutation was identified in an Australian family; this mutation is reported to generate an increase of Aβ42 peptide levels in CHO cells.[91] The majority of EOFAD mutations alter processing of APP in such a way that the relative level of Aβ42 is increased by increasing Aβ42, decreasing Aβ40 peptide levels, or increasing Aβ42 while decreasing Aβ40 peptide levels.[73,74]

AD3: Presenilin 1 (PSEN1)

Inheritance and clinical features: Linkage studies[92] established the presence of an AD3 locus on chromosome 14, and positional cloning led to the identification of mutations in the presenilin 1 (*PSEN1*) gene, which encodes a polytopic membrane protein.[93] Presenilins are major components of the atypical aspartyl protease complexes that are responsible for the γ-secretase cleavage of APP.[94,95] Mutations in *PSEN1* are the most common cause of EOFAD. Indeed, *PSEN1* missense mutations account for 18% to 50% of autosomal dominant EOFAD cases.[96] Over 176 different *PSEN1* mutations have been identified in 390 families. *PSEN1* mutations appear to increase the ratio of Aβ42 to Aβ40, thereby resulting in a change in function that leads to reduced γ-secretase activity.[97] It has been suggested that deposition of Aβ42 may be an early preclinical event in *PSEN1* mutation carriers.[98]

Defects in *PSEN1* cause the most severe forms of AD, with complete penetrance and an onset occurring as early as 30 years of age. However, there is a wide variability in age of onset as other *PSEN1*-associated AD cases have a mean age of onset greater than 58 years. *PSEN1*-associated AD is an autosomal dominant neurodegenerative disorder characterized by progressive dementia and parkinsonism, notch signaling modulation, and Aβ intracellular domain generation.[18,99] There is also considerable phenotypic variability in patients with *PSEN1*-associated AD, including some patients who develop spastic paraparesis and other atypical AD symptoms. Some of these variable clinical phenotypes have been associated with specific mutations. Neuropathogical studies often confirm the clinical diagnosis of AD with measurement of amyloid plaque and Braak stage (as described above) as well as other neurodegenerative changes in other brain areas according to the presence of specific *PSEN1* mutations.[100,101] For example, researchers found that the clinical and neuropathologic features of a Greek family with a *PSEN1* mutation (N135S) included memory loss when the family members were in their 30s, as well as variable limb spasticity and seizures. On neuropathological examination of these family members, the diagnosis of AD was confirmed, and there was also histological evidence of corticospinal tract degeneration.[101] Moreover, a *PSEN1* mutation (I143M) that lies in a cluster in the second transmembrane domain of the protein has been described in an African family with an age at onset in the early 50s and a short duration of illness for 6 to 7 years. These family members were diagnosed on autopsy with severe AD pathology characterized by neuronal loss, abundant Aβ neuritic plaques and neurofibrillary tangles, and degeneration extending into the brain stem.[102]

Gene location and structure: *PSEN1* is located on chromosome 14q24.2. It consists of 12 exons that encode a 467-amino-acid protein that is predicted to traverse the membrane 6 to 10 times; the amino and carboxyl termini are both oriented toward the cytoplasm.[103]

Gene function and expression: *PSEN1* is a polytopic membrane protein that forms the catalytic core of the γ-secretase complex.[94,104] γ-secretase is an integral membrane protein typically found at the cell surface, but it may also be found in the Golgi, endoplasmic reticulum, and mitochondria.[94,105]

PSEN1, nicastrin (Nct), anterior pharynx defective 1 (Aph-1), and presenilin enhancer 2 (PSENEN) are required for the stability and activity of the γ-secretase complex.[106–110] This complex cleaves many type-I transmembrane proteins, including APP and Notch,[94,111] 2 proteins in the hydrophobic environment of the phospholipid bilayer of the membrane.[109]

PSEN1 knockout (KO) mice are not viable,[112] but a conditional *PSEN1* KO mouse model, where the loss of the gene is limited to the postnatal forebrain, found that KO mice exhibited mild cognitive impairments in long-term spatial reference memory and retention.[113] These findings suggest that presenilins play a role in cognitive memory. Moreover, knockin mice with missense mutations of the endogenous murine *PSEN1* have high Aβ42 levels and perform poorly on the object recognition test.[114,115] Double *PSEN1*/*APP* transgenics have been developed, and these transgenics suggest that *PSEN1*, *APP*, and mutations within these genes play a role in the production of Aβ.[78,116]

Genetic variation: To date, there have been 176 *PSEN1* mutations reported (Figure 3). A comprehensive list of *PSEN1* mutations is available through the NCBI database (http://www.molgen.ua.ac.be/ADmutations). The majority of these mutations are missense mutations. These missense mutations cause amino acid substitutions throughout the PSEN1 protein and appear to result in a relative increase in the ratio of Aβ42 to Aβ40 peptides; this increase seems to occur through increased Aβ42 production, decreased Aβ40 production, or alternatively, a combination of increased Aβ42 production and decreased Aβ40 production.[73] For example, individuals that carry the *PSEN1*-L166P mutation can have an age at onset in adolescence, and in vitro studies indicate that this mutation induces exceptionally high levels of Aβ42 production as well as impaired notch intracellular domain production and notch signaling.[100]

AD4: Presenilin 2 (PSEN2)

Inheritance and clinical features: A candidate gene for the chromosome 1 AD4 locus was identified in 1995 in a Volga German AD kindred with a high homology to the AD3 locus (*PSEN1*); this gene was later named presenilin 2 (*PSEN2*).[51,117,118] In contrast to the mutations in the *PSEN1* gene, missense mutations in the *PSEN2* gene are a rare cause of EOFAD, at least in Caucasian populations. The clinical features of PSEN2-affected families appear to differ from the clinical features of PSEN1-affected families in that the age of onset in these family members is generally older (45–88 years) than for some family members with *PSEN1* mutations (25–65 years). Furthermore, the age of onset is highly variable among PSEN2-affected members of the same family; whereas in families with *PSEN1* mutations, the age of onset is generally quite similar among affected family members, and it is even similar among people from different families with the same mutation.[5,51,93,117] Missense mutations in the *PSEN2* gene may be of lower penetrance than in the *PSEN1* gene and therefore may be subject to the modifying action of other genes or environmental influences.[51,119]

Gene location and structure: The*PSEN2* gene is located on chromosome 1 (1q42.13) and was identified by sequence homology and then cloned.[117,118] *PSEN2* has 12 exons and is organized into 10 translated exons that encode a 448-amino-acid peptide. The PSEN2 protein is predicted to consist of 9 transmembrane domains and a large loop structure between the sixth and seventh domains (Figure 4). *PSEN2* also displays tissue-specific alternative splicing.[117,118,120–122]

Gene function and expression: Like *PSEN1*, *PSEN2* has been described as a component of the atypical aspartyl protease called γ-secretase, which is responsible for the cleavage of Aβ.[94,95] *PSEN2* is expressed in a variety of tissues, including the brain, where it is expressed primarily in neurons.[123] *PSEN2*-associated mutations have been reported to increase the ratio of Aβ42 to Aβ40 (Aβ42/Aβ40) in mice and humans,[73,97] indicating that presenilins might modify the way in which γ-secretase cuts APP.

Amyloid precursor protein processing at the γ-secretase site has been reported to be differentially affected by specific presenilin mutations. For example, *PSEN1*-L166P mutations cause a reduction in Aβ production whereas *PSEN1*-G384A mutations significantly increase Aβ42. In contrast, PSEN2 appears to be a less efficient producer of Aβ than PSEN1.[25] The functions and biological importance of presenilin splice variants are poorly understood, but it appears that differential expression of presenilin isoforms may lead to differential regulation of the proteolytic processing of the APP. For example, aberrant *PSEN2* transcripts lacking exon 5 appear to increase the rate of production of Aβ peptide,[124] whereas naturally occurring isoforms without exons 3 and 4 and/or without exon 8 do not affect production of Aβ.[125]

Genetic variation: Mutations in PSEN2 are a much rarer cause of familial AD than are *PSEN1* mutations; *PSEN2* mutations have been described in 6 families, including the Volga-German kindred where a founder effect has been demonstrated,[50,51,117,118] whereas *PSEN1* mutations have been found in 390 families. To date, as many as 14 *PSEN2* mutations have been identified. One of the first mutations to be identified was a point mutation located within the second transmembrane domain that resulted in the substitution of an isoleucine for an asparagine at residues 141 (N141l).[118] Most recently, a V393M mutation located within the seventh transmembrane domain has been described126 (Figure 4). A comprehensive list of *PSEN2* mutations is available through the NCBI database (http://www.molgen.ua.ac.be/ADmutations).

Genes Associated With Risk in Sporadic AD

AD2: APOE

Inheritance and clinical features: The *APOE* gene has been associated with both familial late-onset and sporadic late-onset AD in numerous studies of multiple ethnic groups. The *APOE* ε4 genotype is associated with higher risk of AD,[127] earlier age of onset of both AD[128] and Down syndrome (where there is an additional copy of chromosome 21 carrying the *APP* gene),[129] and a worse outcome after head trauma[130] and stroke, both in humans[131] and in transgenic mice expressing human *APOE* ε4.[132] The frequency of the *APOE* ε4 allele varies between ethnic groups, but regardless of ethnic group, *APOE* ε4− carriers are more frequently found in controls and *APOE* ε4+ carriers are more frequently found in patients with AD.[39–41,133–142]

Gene location and structure: The *APOE* gene is located on chromosome 19q13.2 and consists of 4 exons that encode a 299-amino-acid protein. The *APOE* gene is in a cluster with other apolipoprotein genes: *APOC1*, *APOC2*, and *APOC4*. The *APOE* ε4 loci are located within exon 4 of the gene. The 3 *APOE* ε4 alleles (ε2, ε3, and ε4) are defined by 2 single nucleotide polymorphisms, rs429358 and rs7412, which encode 3 protein isoforms (E2, E3, and E4). The most frequent apoE isoform is apoE3, which contains cysteine and arginine at amino acid positions 112 and 158. In contrast, these positions contain only cysteine residues in apoE2 and only arginine residues in apoE4 (Figure 5). The cysteine-arginine substitution affects the 3-dimensional structure and the lipid-binding properties between isoforms. In apoE4, the amino acid substitution results in the formation of a salt bridge between an arginine in position 61 and a glutamic acid in 255; whereas apoE3 and

apoE2 bind preferentially to high-density lipoproteins (HDLs), this changed structure causes the apoE4 isoform to bind preferentially to very-low-density lipoproteins (VLDLs).[143]

Gene function and expression: The mechanisms that govern apoE toxicity in brain tissue are not fully understood. Some proposed mechanisms include isoform-specific toxicity, *APOE* ε4-mediated amyloid aggregation, and *APOE* ε4-mediated tau hyperphosphorylation.[144]

The *APOE* polymorphism is unique to humans and has been proposed to have evolved as a result of adaptive changes to diet.[145,146] It is known that apoE plays an important role in the distribution and metabolism of cholesterol and triglycerides within many organs and cell types in the human body.[143] Individuals carrying *APOE* ε4 have higher total and LDL cholesterol.[147] Moreover, in vitro neurons have a cholesterol uptake that is lower when lipids are bound to apoE4 compared to apoE2 and apoE3,[148] and apoE4 appears to be less efficient than the other isoforms in promoting cholesterol efflux from both neurons and astrocytes.[149]

As the major apolipoprotein of the chylomicron in the brain, apoE binds to a specific receptor and works through receptor-mediated endocytosis to rapidly remove chylomicron and VLDL remnants from circulation; this process is essential for the normal catabolism of triglyceride-rich lipoprotein constituents.[150] In the brain, lipidated apoE binds aggregated Aβ in an apoE isoform-specific manner, with apoE4 being much more effective than the apoE3 isoform. Researchers have also proposed that the more efficient binding process of apoE4 enhances the deposition of the Aβ peptide.[151]

Brain cells from *APOE* knockout (*APOE*−/−) mice are more sensitive to excitotoxic and age-related synaptic loss,152 and Aβ-induced synaptosomal dysfunction in these mice is also enhanced compared to control animals.[153] When human apoE isoforms (apoE3 and apoE4) are expressed in *APOE*−/− mice, the expression of apoE3, but not apoE4, is protective against age-related neurodegeneration[152] and Aβ toxicity.[153] In addition, astrocytes from *APOE* −/− mice that express human apoE3 release more cholesterol than those expressing apoE4; this suggests that apoE isoforms may modulate the amount of lipid available for neurons. Other studies report apoE-specific effects on Aβ removal from the extracellular space, whereby the apoE3 isoform has a higher Aβ-binding capacity than apoE4.[154,155] Animal and in vitro models show that, in the brain, astrocytes and microglia are the main producers of secreted apoE.[156,157] ApoE secretion in human primary astrocytes can be reduced by a combination of cytokines[158]; whereas under stress conditions, neurons appear to be the main producers of apoE.[159,160] In a rodent model, moderate injury has been shown to induce enhancement of apoE levels in clusters of CA1 and CA3 pyramidal neurons,[161] and in another rodent model, apoE levels have been shown to increase in response to peripheral nerve injury.[162]

In addition, individuals carrying *APOE* ε4 have higher amyloid and tangle pathology[163] and an increase in mitochondrial damage[164] compared to those carrying other *APOE* polymorphisms.

Genetic variation: The gene dose of *APOE* ε4 is a major risk factor for AD, with many studies reporting an association between gene dose, age at onset,[165] and cognitive decline.[166] After age 65, the risk of AD among individuals with a family member with AD increases depending on the number of ε4 alleles present in the affected individual. Risks to family members with the *APOE* 2/2 and 2/3 genotypes are nearly identical at all ages to risks for family members with the *APOE* 3/3 genotype. Among family members with *APOE* 3/3, the lifetime risk of AD by age 90 can be as much as 3 times greater than the expected risk found

in *APOE* ε4 carriers, suggesting that factors other than *APOE* contribute to AD risk. In addition, a 44% risk of AD by age 93 among family members of *APOE* 4/4 carriers indicates that as many as 50% of people having at least 1 ε4 allele do not develop AD. There also appears to be a gender modification effect because the risk to male family members with *APOE* 3/4 is similar to that for the *APOE* 3/3 carriers but is significantly less than the risk for the *APOE* 4/4 carriers, whereas among female family members, the risk for the *APOE* 3/4 carriers is nearly twice that for the *APOE* 3/3 carriers.[134–142]

Summary

Alzheimer disease is characterized by an irreversible, progressive loss of memory and cognitive skills that can occur in rare familial cases as early as the third decade. Currently, there is no cure for AD, and treatments only manage to slow down the progression of AD in some patients.[11,12] The early-onset familial forms of AD have an autosomal dominant inheritance linked to 3 genes: *APP*, *PSEN1*, and *PSEN2*, whereas the most common sporadic form of AD, which occurs after the age of 60, has thus far been consistently, across numerous studies, associated with only 1 gene, the *APOE* gene. The mechanistic contribution of these genes in AD pathogenesis has been studied extensively, but the specific biology involved in the progression of AD remains unclear, suggesting that AD is a genetic and environmentally complex disease.

Genetic Testing and Counseling

APOE ε4 is most highly associated with AD for individuals with a family history of dementia, and this association is highest for individuals that carry 2 *APOE* ε4 alleles (ε4/ε4 genotypes). The ε4/ε4 genotype is uncommon, and although the ethnicity of the population may alter the expected prevalence, the genotype occurs in about 1% of normal Caucasian controls. In contrast, the ε4/ε4 genotype occurs in nearly 19% of familial LOAD populations. *APOE* ε4-associated risk is also found in African Americans and Caribbean Hispanics.[167,168] Women with an *APOE* ε4/ε4 genotype have a 45% probability of developing AD by age 73,[169] whereas men have a 25% risk of developing AD by that age.[170] Alzheimer disease risk is also lower for individuals with only 1 *APOE* ε4 allele (by age 87) or no *APOE* ε4 allele (by age 95).[170] Approximately 42% of persons with LOAD do not have an *APOE* ε4 allele.[171] Thus, the absence of the *APOE ε4* allele does not rule out a LOAD diagnosis. First-degree relatives of a person with LOAD have a cumulative lifetime risk of approximately 20% to 25%, whereas the risk in the general population is 10.4%.[141,172] It is still not known whether the age of onset of a patient with LOAD changes the risk to first-degree relatives. However, the number of additional affected family members most likely increases the risk in close relatives.[173] Given the low predictive value of the *APOE ε4* allele, the general consensus is that *APOE* genetic testing has limited value in asymptomatic persons for predicting AD risk.[174,175] Family history may, therefore, be a better predictor of LOAD risk.[173]

In contrast, EOFAD, with an age at onset before 60 to 65 years old, has an autosomal dominant mode of inheritance in which 20% to 70% of cases are estimated to have a *PSEN1* mutation, 10% to 15% of cases are estimated to have an *APP* mutation, and *PSEN2* mutations are rare.[174,176] Indeed, approximately 60% of patients with EOAD have another known affected family member. The remaining 40% of patients with EOAD may lack a family history because of an early death of a parent, failure to recognize the disorder in family members, or, very rarely, a de novo mutation.[5] If the parent of a patient with EOAD has a mutant allele, then the risk to the patient's sibling of inheriting the mutant allele is 50%. The child of a patient with EOAD who carries a mutation (*APP*, *PSEN1*, or *PSEN2*) has a 50% chance of transmitting the mutant allele to each of their children.

Testing of asymptomatic adults who are at risk for EOAD caused by mutations in the *PSEN1*, *PSEN2*, or *APP* genes is available clinically. However, genetic testing results for at-risk asymptomatic adults can only be interpreted after the disease-causing mutation has first been identified in the affected family member. It should be emphasized that testing of asymptomatic at-risk individuals with nonspecific or equivocal symptoms is predictive not diagnostic. In addition, obtaining results from genetic testing can affect an individual's personal relationships as well as their emotional well-being, and it may even cause depression. The principal arguments against testing asymptomatic individuals during childhood are that the testing then removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications. Thus, the general consensus is that individuals who are at risk for adult-onset disorders should not be tested during childhood. Prenatal genetic testing for mutations in the *PSEN1* gene is possible if the *PSEN1* allele has been identified in an affected family member first. Preimplantation genetic diagnosis is also available for families that have a disease-causing mutation. However, parental requests for prenatal or preimplantation genetic testing of adult-onset diseases are rare.[4]

In this article, we have reviewed the genetics of AD. Further molecular genetic investigations should clarify the roles of additional known genes in the pathogenesis of both common sporadic as well as rare familial forms of AD. Already, investigations of the normal and aberrant functions of Aβ protein and ApoE has provided insight into the underlying mechanisms for AD. Such research will continue to provide new strategies for therapeutic interventions.

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References

1. Mayeux R. Epidemiology of neurodegeneration. Annu Rev Neurosci 2003;26(6):81–104. [PubMed: 12574495]
2. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005;366(9503):2112–2117. [PubMed: 16360788]
3. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. Arch Neurol 2002;59(11):1737–1746. [PubMed: 12433261]
4. Bird TD. Genetic aspects of Alzheimer disease. Genet Med 2008;10(4):231–239. [PubMed: 18414205]
5. Campion D, Dumanchin C, Hannequin D, et al. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. Am J Hum Genet 1999;65(3):664–670. [PubMed: 10441572]
6. Brickell KL, Steinbart EJ, Rumbaugh M, et al. Early-onset Alzheimer disease in families with late-onset Alzheimer disease: a potential important subtype of familial Alzheimer disease. Arch Neurol 2006;63(9):1307–1311. [PubMed: 16966510]

7. Roses AD. On the discovery of the genetic association of Apolipoprotein E genotypes and common late-onset Alzheimer disease. J Alzheimers Dis 2006;9(3):361–366. [PubMed: 16914873]
8. Kamboh MI. Molecular genetics of late-onset Alzheimer's disease. Ann Hum Genet 2004;68(4): 381–404. [PubMed: 15225164]
9. Bertram L, Tanzi RE. The current status of Alzheimer's disease genetics: what do we tell the patients? Pharmacol Res 2004;50(4):385–396. [PubMed: 15304236]
10. Serretti A, Artioli P, Quartesan R, De Ronchi D. Genes involved in Alzheimer's disease, a survey of possible candidates. J Alzheimers Dis 2005;7(4):331–353. [PubMed: 16131736]
11. Raschetti R, Albanese E, Vanacore N, Maggini M. Cholinesterase inhibitors in mild cognitive impairment: a systematic review of randomised trials. PLoS Med 2007;4(11):e338. [PubMed: 18044984]
12. Raina P, Santaguida P, Ismaila A. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med 2008;148(5): 379–397. [PubMed: 18316756]
13. Kawas CH. Clinical practice. early Alzheimer's disease. N Engl J Med 2003;349(11):1056–1063. [PubMed: 12968090]
14. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34(7):939–944. [PubMed: 6610841]
15. Rogan S, Lippa CF. Alzheimer's disease and other dementias: a review. Am J Alzheimers Dis Other Demen 2002;17(6):11–17. [PubMed: 11831415]
16. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18(4):351–357. [PubMed: 9330961]
17. Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. N Engl J Med 2003;348(14):1356–1364. [PubMed: 12672864]
18. Goedert M, Spillantini MG. A century of Alzheimer's disease. Science 2006;314(5800):777–781. [PubMed: 17082447]
19. Kaye JA. Diagnostic challenges in dementia. Neurology 1998;51(1):S45–S52. discussion S65–S67. [PubMed: 9674762]
20. Mirra SS, Gearing M, McKeel DW Jr, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41(4):479–486. [PubMed: 2011243]
21. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82(4):239–259. [PubMed: 1759558]
22. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Neurobiol Aging 1997;18(4):S1–S2. [PubMed: 9330978]
23. Glenner GG, Wong CW, Quaranta V, Eanes ED. The amyloid deposits in Alzheimer's disease: their nature and pathogenesis. Appl Pathol 1984;2(6):357–369. [PubMed: 6242724]
24. Iwatsubo T, Odaka A, Suzuki N, Mizusawa H, Nukina N, Ihara Y. Visualization of A beta 42(43) and A beta 40 in senile plaques with end-specific A beta monoclonals: evidence that an initially deposited species is A beta 42(43). Neuron 1994;13(1):45–53. [PubMed: 8043280]
25. Bentahir M, Nyabi O, Verhamme J, et al. Presenilin clinical mutations can affect gamma-secretase activity by different mechanisms. J Neurochem 2006;96(3):732–742. [PubMed: 16405513]
26. Haass C, Koo EH, Mellon A, Hung AY, Selkoe DJ. Targeting of cell-surface beta-amyloid precursor protein to lysosomes: alternative processing into amyloid-bearing fragments. Nature 1992;357(6378):500–503. [PubMed: 1608449]
27. Seubert P, Vigo-Pelfrey C, Esch F, et al. Isolation and quantification of soluble Alzheimer's beta-peptide from biological fluids. Nature 1992;359(6393):325–327. [PubMed: 1406936]
28. Shoji M, Golde T, Ghiso J, et al. Production of the Alzheimer amyloid beta protein by normal proteolytic processing. Science 1995;258(5078):126–129. [PubMed: 1439760]

29. Cai H, Wang Y, McCarthy D, et al. BACE1 is the major beta-secretase for generation of Abeta peptides by neurons. Nat Neurosci 2001;4(3):233–234. [PubMed: 11224536]
30. Vassar R, Bennett BD, Babu-Khan S, et al. Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science 1999;286(5443):735–741. [PubMed: 10531052]
31. De Strooper B. Alzheimer's disease. Closing in on gamma-secretase. Nature 2000;405(6787):627. 629. [PubMed: 10864307]
32. Schroeter EH, Ilagan MX, Brunkan AL, et al. A presenilin dimer at the core of the gamma-secretase enzyme: insights from parallel analysis of Notch 1 and APP proteolysis. Proc Natl Acad Sci U S A 2003;100(22):13075–13080. [PubMed: 14566063]
33. Irvine GB, El-Agnaf OM, Shankar GM, Walsh DM. Protein aggregation in the brain: the molecular basis for Alzheimer's and Parkinson's diseases. Mol Med 2008;14(7–8):451–464. [PubMed: 18368143]
34. Kosik KS, Bakalis SF, Selkoe DJ, Pierce MW, Duffy LK. High molecular weight microtubule-associated proteins: purification by electro-elution and amino acid compositions. J Neurosci Res 1986;15(4):543–551. [PubMed: 2873254]
35. Wood JG, Mirra SS, Pollock NJ, Binder LI. Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau). Proc Natl Acad Sci U S A 1986;83(11) 4040-1043.
36. Braak H, Braak E. Demonstration of amyloid deposits and neurofibrillary changes in whole brain sections. Brain Pathol 1991;1(3):213–216. [PubMed: 1669710]
37. Thal DR, Capetillo-Zarate E, Del Tredici K, Braak H. The development of amyloid beta protein deposits in the aged brain. Sci Aging Knowledge Environ 2006;2006 re1.
38. Bertram L, Tanzi RE. Alzheimer's disease: one disorder, too many genes? Hum Mol Genet 2004;13(1):R135–R141. [PubMed: 14764623]
39. Roses AD, Saunders AM, Alberts MA, et al. Apolipoprotein E E4 allele and risk of dementia. JAMA 1995;273:374–375. author reply 375–l376. [PubMed: 7823377]
40. Schellenberg GD. Genetic dissection of Alzheimer disease, heterogeneous disorder. Proc Natl Acad Sci U S A 1995;92(19):8552–8559. [PubMed: 7567974]
41. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev 2001;81(2):741–766. [PubMed: 11274343]
42. Couzin J. Genetics. Once shunned, test for Alzheimer's risk headed to market. Science 2008;319(5866):1022–1023. [PubMed: 18292309]
43. Coon KD, Myers AJ, Craig DW, et al. A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. J Clin Psychiatry 2007;68(4):613–618. [PubMed: 17474819]
44. Chai CK. The genetics of Alzheimer's disease. Am J Alzheimers Dis Other Demen 2007;22(1):37–41. [PubMed: 17534000]
45. Daw EW, Payami H, Nemens EJ, et al. The number of trait loci late-onset Alzheimer disease. Am J Hum Genet 2000;66(1):196–204. [PubMed: 10631151]
46. Kang J, Lemaire HG, Unterbeck A, et al. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature 1987;325(6106):733–736. [PubMed: 2881207]
47. Giaccone G, Tagliavini F, Linoli G, et al. Down patients: extracellular preamyloid deposits precede neuritic degeneration and senile plaques. Neurosci Lett 1989;97(1–2):232–238. [PubMed: 2521927]
48. Mann DM, Prinja D, Davies CA, et al. Immunocytochemical profile of neurofibrillary tangles in Down's syndrome patients of different ages. J Neurol Sci 1989;92(2–3):247–260. [PubMed: 2553874]
49. Lemere CA, Blusztajn JK, Yamaguchi H, Wisniewski T, Saido TC, Selkoe DJ. Sequence of deposition of heterogeneous amyloid beta-peptides and APO E in Down syndrome: implications for initial events in amyloid plaque formation. Neurobiol Dis 1996;3(1):16–32. [PubMed: 9173910]
50. Cruts M, Van Broeckhoven C. Molecular genetics of Alzheimer's disease. Ann Med 1998;30(6): 560–565. [PubMed: 9920359]

51. Sherrington R, Froelich S, Sorbi S, et al. Alzheimer's disease associated with mutations in presenilin 2 is rare and variably penetrant. Hum Mol Genet 1996;5(7):985–988. [PubMed: 8817335]
52. Janssen JC, Beck JA, Campbell TA, et al. Early onset familial Alzheimer's disease: mutation frequency in 31 families. Neurology 2003;60(2):235–239. [PubMed: 12552037]
53. Raux G, Guyant-Marechal L, Martin C, et al. Molecular diagnosis of autosomal dominant early onset Alzheimer's disease: an update. J Med Genet 2005;42(10):793–795. [PubMed: 16033913]
54. Suzuki N, Cheung TT, Cai XD, et al. An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (beta APP717) mutants. Science 1994;264(5163):1336–1340. [PubMed: 8191290]
55. Esler WP, Wolfe MS. A portrait of Alzheimer secretases–new features and familiar faces. Science 2001;293(5534):1449–1454. [PubMed: 11520976]
56. Hardy J. The genetic causes of neurodegenerative diseases. J Alzheimers Dis 2001;3(1):109–116. [PubMed: 12214079]
57. Goldgaber D, Lerman MI, McBride OW, Saffiotti U, Gajdusek DC. Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease. Science 1987;235(4791):877–880. [PubMed: 3810169]
58. Tanzi RE, Haines JL, Watkins PC, et al. Protease inhibitor domain encoded by an amyloid protein precursor mRNA associated with Alzheimer's disease. Nature 1988;331(6156):528–530. [PubMed: 2893290]
59. Ponte P, Gonzalez-DeWhitt P, Schilling J, et al. A new A4 amyloid mRNA contains a domain homologous to serine proteinase inhibitors. Nature 1988;331(6156):525–527. [PubMed: 2893289]
60. Kitaguchi N, Takahashi Y, Tokushima Y, Shiojiri S, Ito H. Novel precursor of Alzheimer's disease amyloid protein shows protease inhibitory activity. Nature 1988;331(6156):530–532. [PubMed: 2893291]
61. Golde TE, Estus S, Usiak M, Younkin LH, Younkin SG. Expression of beta amyloid protein precursor mRNAs: recognition of a novel alternatively spliced form and quantitation in Alzheimer's disease using PCR. Neuron 1990;4(2):253–267. [PubMed: 2106330]
62. de Sauvage F, Octave JN. A novel mRNA of the A4 amyloid precursor gene coding for a possibly secreted protein. Science 1989;245(4918):651–653. [PubMed: 2569763]
63. Yoshikai S, Sasaki H, Doh-ura K, Furuya H, Sakaki Y. Genomic organization of the human amyloid beta-protein precursor gene. Gene 1990;87(2):257–263. [PubMed: 2110105]
64. Turner PR, O'Connor K, Tate WP, Abraham WC. Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. Prog Neurobiol 2003;70(1):1–32. [PubMed: 12927332]
65. Priller C, Bauer T, Mitteregger G, Krebs B, Kretzschmar HA, Herms J. Synapse formation and function is modulated by the amyloid precursor protein. J Neurosci 2006;26(27):7212–7221. [PubMed: 16822978]
66. Koo EH, Squazzo SL. Evidence that production and release of amyloid beta-protein involves the endocytic pathway. J Biol Chem 1994;269(26):17386–17389. [PubMed: 8021238]
67. Bossy-Wetzel E, Schwarzenbacher R, Lipton SA. Molecular pathways to neurodegeneration. Nat Med 2004;10(1):S2–S9. [PubMed: 15272266]
68. Devi L, Prabhu BM, Galati DF, Avadhani NG, Anandatheerthavarada HK. Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. J Neurosci 2006;26(35):9057–9068. [PubMed: 16943564]
69. Lin MT, Beal MF. Alzheimer's APP mangles mitochondria. Nat Med 2006;12(11):1241–1243. [PubMed: 17088888]
70. Anandatheerthavarada HK, Biswas G, Robin MA, Avadhani NG. Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. J Cell Biol 2003;161(1):41–54. [PubMed: 12695498]
71. Walter J, Kaether C, Steiner H, Haass C. The cell biology of Alzheimer's disease: uncovering the secrets of secretases. Curr Opin Neurobiol 2001;11(5):585–590. [PubMed: 11595492]

72. Sastre M, Steiner H, Fuchs K, et al. Presenilin-dependent gamma-secretase processing of beta-amyloid precursor protein at a site corresponding to the S3 cleavage of Notch. EMBO Rep 2001;2(9):835–841. [PubMed: 11520861]
73. Scheuner D, Eckman C, Jensen M, et al. Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. Nat Med 1996;2(8):864–870. [PubMed: 8705854]
74. Walker LC, Ibegbu CC, Todd CW, et al. Emerging prospects for the disease-modifying treatment of Alzheimer's disease. Biochem Pharmacol 2005;69(7):1001–1008. [PubMed: 15763538]
75. Goate A, Chartier-Harlin MC, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 1991;349(6311):704–706. [PubMed: 1671712]
76. Mullan M. Familial Alzheimer's disease: second gene locus located. BMJ 1992;305(6862):1108–1109. [PubMed: 1463941]
77. Higgins GA, Jacobsen H. Transgenic mouse models of Alzheimer's disease: phenotype and application. Behav Pharmacol 2003;14(5–6):419–438. [PubMed: 14501255]
78. Mineur YS, McLoughlin D, Crusio WE, Sluyter F, Huynh LX. Genetic mouse models of Alzheimer's disease Social behavior deficits in the Fmr1 mutant mouse Genetic dissection of learning and memory in mice. Neural Plast 2005;12(4):299–310. [PubMed: 16444901]
79. Irizarry MC, McNamara M, Fedorchak K, Hsiao K, Hyman BT. APPSw transgenic mice develop age-related A beta deposits and neuropil abnormalities, but no neuronal loss in CA1. J Neuropathol Exp Neurol 1997;56(9):965–973. [PubMed: 9291938]
80. Westerman MA, Cooper-Blacketer D, Mariash A, et al. The relationship between Abeta and memory in the Tg2576 mouse model of Alzheimer's disease. J Neurosci 2002;22(5):1858–1867. [PubMed: 11880515]
81. Weidemann A, König G, Bunke D, et al. Identification, biogenesis, and localization of precursors of Alzheimer's disease A4 amyloid protein. Cell 1989;57(1):115–126. [PubMed: 2649245]
82. Sandbrink R, Masters CL, Beyreuther K. Similar alternative splicing of a non-homologous domain in beta A4-amyloid protein precursor-like proteins. J Biol Chem 1994;269(19):14227–14234. [PubMed: 8188705]
83. Lemaire HG, Salbaum JM, Multhaup G, et al. The PreA4(695) precursor protein of Alzheimer's disease A4 amyloid is encoded by 16 exons. Nucleic Acids Res 1989;17(2):517–522. [PubMed: 2783775]
84. Konig G, Salbaum JM, Wiestler O, et al. Alternative splicing of the beta A4 amyloid gene of Alzheimer's disease in cortex of control and Alzheimer's disease patients. Brain Res Mol Brain Res 1991;9(3):259–262. [PubMed: 1851528]
85. Palmert MR, Golde TE, Cohen ML, et al. Amyloid protein precursor messenger RNAs: differential expression in Alzheimer's disease. Science 1988;241(4869):1080–1084. [PubMed: 2457949]
86. Neve RL, Finch EA, Dawes LR. Expression of the Alzheimer amyloid precursor gene transcripts in the human brain. Neuron 1988;1(8):669–677. [PubMed: 2908447]
87. Johnson SA, Rogers J, Finch CE. APP-695 transcript prevalence is selectively reduced during Alzheimer's disease in cortex and hippocampus but not in cerebellum. Neurobiol Aging 1989;10(6):755–760. [PubMed: 2483450]
88. Tanaka S, Nakamura S, Ueda K, et al. Three types of amyloid protein precursor mRNA in human brain: their differential expression in Alzheimer's disease. Biochem Biophys Res Commun 1988;157(2):472–479. [PubMed: 3144271]
89. Sisodia SS, Koo EH, Beyreuther K, Unterbeck A, Price DL. Evidence that beta-amyloid protein in Alzheimer's disease is not derived by normal processing. Science 1990;248(4954):492–495. [PubMed: 1691865]
90. Jacobsen JS, Muenkel HA, Blume AJ, Vitek MP. A novel species-specific RNA related to alternatively spliced amyloid precursor protein mRNAs. Neurobiol Aging 1991;12(5):575–583. [PubMed: 1722873]
91. Kwok JB, Li QX, Hallupp M, et al. Novel Leu723Pro amyloid precursor protein mutation increases amyloid beta42(43) peptide levels and induces apoptosis. Ann Neurol 2000;47(2):249–253. [PubMed: 10665499]

92. Schellenberg GD, Bird TD, Wijsman EM, et al. Genetic linkage evidence for a familial Alzheimer's disease locus on chromosome 14. Science 1992;258(5082):668–671. [PubMed: 1411576]

93. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995;375(6534):754–760. [PubMed: 7596406]

94. De Strooper B, Saftig P, Craessaerts K, et al. Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein. Nature 1998;391(6665):387–390. [PubMed: 9450754]

95. Wolfe MS, Xia W, Ostaszewski BL, Diehl TS, Kimberly WT, Selkoe DJ. Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity. Nature 1999;398(6727):513–517. [PubMed: 10206644]

96. Theuns J, Del-Favero J, Dermaut B, et al. Genetic variability in the regulatory region of presenilin 1 associated with risk for Alzheimer's disease and variable expression. Hum Mol Genet 2000;9(3): 325–331. [PubMed: 10655540]

97. Citron M, Westaway D, Xia W, et al. Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid beta-protein in both transfected cells and transgenic mice. Nat Med 1997;3(1):67–72. [PubMed: 8986743]

98. Lippa CF, Nee LE, Mori H, St George-Hyslop P. Abeta-42 deposition precedes other changes in PS-1 Alzheimer's disease. Lancet 1998;352(9134):1117–1118. [PubMed: 9798591]

99. Wolfe MS. When loss is gain: reduced presenilin proteolytic function leads to increased Abeta42/Abeta40. Talking Point on the role of presenilin mutations in Alzheimer disease. EMBO Rep 2007;8(2):136–140. [PubMed: 17268504]

100. Moehlmann T, Winkler E, Xia X, et al. Presenilin-1 mutations of leucine 166 equally affect the generation of the Notch and APP intracellular domains independent of their effect on Abeta 42 production. Proc Natl Acad Sci U S A 2002;99(12):8025–8030. [PubMed: 12048239]

101. Rudzinski LA, Fletcher RM, Dickson DW, et al. Early onset familial Alzheimer Disease with spastic paraparesis, dysarthria, and seizures and N135S mutation in PSEN1. Alzheimer Dis Assoc Disord 2008;22(3):299–307. [PubMed: 18580586]

102. Heckmann JM, Low WC, de Villiers C, et al. Novel presenilin 1 mutation with profound neurofibrillary pathology in an indigenous Southern African family with early-onset Alzheimer's disease. Brain 2004;127(pt 1):133–142. [PubMed: 14570818]

103. Hutton M, Hardy J. The presenilins and Alzheimer's disease. Hum Mol Genet 1997;6(10):1639–1646. [PubMed: 9300655]

104. Wolfe MS, De Los Angeles J, Miller DD, Xia W, Selkoe DJ. Are presenilins intramembrane-cleaving proteases? Implications for the molecular mechanism of Alzheimer's disease. Biochemistry 1999;38(35):11223–11230. [PubMed: 10471271]

105. Baulac S, LaVoie MJ, Kimberly WT. Functional gamma-secretase complex assembly in Golgi/trans-Golgi network: interactions among presenilin, nicastrin, Aph1, Pen-2, and gamma-secretase substrates. Neurobiol Dis 2003;14(2):194–204. [PubMed: 14572442]

106. Francis R, McGrath G, Zhang J, et al. aph-1 and pen-2 are required for Notch pathway signaling, gamma-secretase cleavage of betaAPP, and presenilin protein accumulation. Dev Cell 2002;3(1): 85–97. [PubMed: 12110170]

107. Goutte C, Tsunozaki M, Hale VA, Priess JR. APH-1 is a multipass membrane protein essential for the Notch signaling pathway in Caenorhabditis elegans embryos. Proc Natl Acad Sci U S A 2002;99(2):775–779. [PubMed: 11792846]

108. Edbauer D, Winkler E, Regula JT, Pesold B, Steiner H, Haass C. Reconstitution of gamma-secretase activity. Nat Cell Biol 2003 May;5(5):486–488. [PubMed: 12679784]

109. Kimberly WT, LaVoie MJ, Ostaszewski BL, Ye W, Wolfe MS, Selkoe DJ. Gamma-secretase is a membrane protein complex comprised of presenilin, nicastrin, Aph-1, and Pen-2. Proc Natl Acad Sci U S A 2003;100(11):6382–6387. [PubMed: 12740439]

110. Takasugi N, Tomita T, Hayashi I, et al. The role of presenilin cofactors in the gamma-secretase complex. Nature 2003;422(6930):438–441. [PubMed: 12660785]

111. De Strooper B, Annaert W, Cupers P, et al. A presenilin-1-dependent gamma-secretase-like protease mediates release of notch intracellular domain. Nature 1999;398(6727):518–522. [PubMed: 10206645]

112. Shen J, Bronson RT, Chen DF, Xia W, Selkoe DJ, Tonegawa S. Skeletal and CNS defects in presenilin-1-deficient mice. Cell 1997;89(4):629–639. [PubMed: 9160754]
113. Yu H, Saura CA, Choi SY, et al. APP processing and synaptic plasticity in presenilin-1 conditional knockout mice. Neuron 2001;31(5):713–726. [PubMed: 11567612]
114. Huang XG, Yee BK, Nag S, Chan ST, Tang F. Behavioral and neurochemical characterization of transgenic mice carrying the human presenilin-1 gene with or without the leucine-to-proline mutation at codon 235. Exp Neurol 2003;183(2):673–681. [PubMed: 14552909]
115. Janus C, D'Amelio S, Amitay O, et al. Spatial learning in transgenic mice expressing human presenilin 1 (PS1) transgenes. Neurobiol Aging 2000;21(4):541–549. [PubMed: 10924767]
116. Holcomb L, Gordon MN, McGowan E, et al. Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. Nat Med 1998;4(1):97–100. [PubMed: 9427614]
117. Rogaev EI, Sherrington R, Rogaeva EA, et al. 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(6543):775–778. [PubMed: 7651536]
118. Levy-Lahad E, Wasco W, Poorkaj P, et al. A familial Alzheimer's disease locus on chromosome 1. Science 1995;269(5226):970–973. [PubMed: 7638621]
119. Tandon A, Fraser P. The presenilins. Genome Biol 2002;3 reviews 3014.
120. Hutton M, Busfield F, Wragg M, et al. Complete analysis of the presenilin 1 gene in early onset Alzheimer's disease. Neuroreport 1996;7(3):801–805. [PubMed: 8733749]
121. Prihar G, Fuldner RA, Perez-Tur J, et al. Structure and alternative splicing of the presenilin-2 gene. Neuroreport 1996;7(10):1680–1684. [PubMed: 8904781]
122. Anwar R, Moynihan TP, Ardley H, et al. Molecular analysis of the presenilin 1 (S182) gene in "sporadic" cases of Alzheimer's disease: identification and characterisation of unusual splice variants. J Neurochem 1996;66(4):1774–1777. [PubMed: 8627338]
123. Kovacs DM, Fausett HJ, Page KJ, et al. Alzheimer-associated presenilins 1 and 2: neuronal expression in brain and localization to intracellular membranes in mammalian cells. Nat Med 1996;2(2):224–229. [PubMed: 8574969]
124. Sato N, Imaizumi K, Manabe T, et al. Increased production of beta-amyloid and vulnerability to endoplasmic reticulum stress by an aberrant spliced form of presenilin 2. J Biol Chem 2001;276(3):2108–2114. [PubMed: 11031265]
125. Grunberg J, Walter J, Eckman C, et al. Truncated presenilin 2 derived from differentially spliced mRNA does not affect the ratio of amyloid beta-peptide 1–42/1–40. Neuroreport 1998;9(14): 3293–3299. [PubMed: 9831466]
126. Lindquist SG, Hasholt L, Bahl JM, et al. A novel presenilin 2 mutation (V393M) in early-onset dementia with profound language impairment. Eur J Neurol 2008;15(10):1135–1139. [PubMed: 18727676]
127. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261(5123):921–923. [PubMed: 8346443]
128. Tang MX, Maestre G, Tsai WY, et al. Relative risk of Alzheimer disease and age-at-onset distributions, based on APOE genotypes among elderly African Americans, Caucasians, and Hispanics in New York City. Am J Hum Genet 1996;58(3):574–584. [PubMed: 8644717]
129. Schupf N, Sergievsky GH. Genetic and host factors for dementia in Down's syndrome. Br J Psychiatry 2002;180:405–410. [PubMed: 11983636]
130. Nicoll JA, Roberts GW, Graham DI. Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. Nat Med 1995;1(2):135–137. [PubMed: 7585009]
131. Liu Y, Laakso MP, Karonen JO, et al. Apolipoprotein E polymorphism and acute ischemic stroke: a diffusion- and perfusion-weighted magnetic resonance imaging study. J Cereb Blood Flow Metab 2002;22(11):1336–1342. [PubMed: 12439291]
132. Horsburgh K, McCulloch J, Nilsen M, Roses AD, Nicoll JA. Increased neuronal damage and apoE immunoreactivity in human apolipoprotein E, E4 isoform-specific, transgenic mice after global cerebral ischaemia. Eur J Neurosci 2000;12(12):4309–4317. [PubMed: 11122341]

133. Chauhan NB. Membrane dynamics, cholesterol homeostasis, and Alzheimer's disease. J Lipid Res 2003;44(11):2019–2029. [PubMed: 12951356]
134. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. Apolipoprotein E polymorphism and Alzheimer's disease. Lancet 1993;342(8873):697–699. [PubMed: 8103819]
135. Tsai MS, Tangalos EG, Petersen RC, et al. Apolipoprotein E: risk factor for Alzheimer disease. Am J Hum Genet 1994;54(4):643–649. [PubMed: 8128961]
136. Lucotte G, Turpin JC, Landais P. Apolipoprotein E-epsilon 4 allele doses in late-onset Alzheimer's disease. Ann Neurol 1994;36(4):681–682. [PubMed: 7944308]
137. Mayeux R, Stern Y, Ottman R, et al. The apolipoprotein epsilon 4 allele in patients with Alzheimer's disease. Ann Neurol 1993;34(5):752–754. [PubMed: 8239575]
138. Liddell M, Williams J, Bayer A, Kaiser F, Owen M. Confirmation of association between the e4 allele of apolipoprotein E and Alzheimer's disease. J Med Genet 1994;31(3):197–200. [PubMed: 8014966]
139. Brousseau T, Legrain S, Berr C, Gourlet V, Vidal O, Amouyel P. Confirmation of the epsilon 4 allele of the apolipoprotein E gene as a risk factor for late-onset Alzheimer's disease. Neurology 1994;44(2):342–344. [PubMed: 8309588]
140. Hendrie HC, Hall KS, Hui S, et al. Apolipoprotein E genotypes and Alzheimer's disease in a community study of elderly African Americans. Ann Neurol 1995;37(1):118–120. [PubMed: 7818244]
141. Farrer LA, Cupples LA, van Duijn CM, et al. Apolipoprotein E genotype in patients with Alzheimer's disease: implications for the risk of dementia among relatives. Ann Neurol 1995;38(5):797–808. [PubMed: 7486872]
142. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997;278(16):1349–1356. [PubMed: 9343467]
143. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc Natl Acad Sci U S A 2006;103(15):5644–5651. Epub 2006 Mar 27. [PubMed: 16567625]
144. Huang Y. Molecular and cellular mechanisms of apolipoprotein E4 neurotoxicity and potential therapeutic strategies. Curr Opin Drug Discov Devel 2006;9(5):627–641.
145. Mahley RW, Rall SC Jr. Is epsilon4 the ancestral human apoE allele? Neurobiol Aging 1999;20(4):429–430. [PubMed: 10604434]
146. Finch CE, Stanford CB. Meat-adaptive genes and the evolution of slower aging in humans. Q Rev Biol 2004;79(1):3–50. [PubMed: 15101252]
147. Sing CF, Davignon J. Role of the apolipoprotein E polymorphism in determining normal plasma lipid and lipoprotein variation. Am J Hum Genet 1985;37(2):268–285. [PubMed: 3985008]
148. Rapp A, Gmeiner B, Huttinger M. Implication of apoE isoforms in cholesterol metabolism by primary rat hippocampal neurons and astrocytes. Biochimie 2006;88(5):473–483. [PubMed: 16376010]
149. Michikawa M, Fan QW, Isobe I, Yanagisawa K. Apolipoprotein E exhibits isoform-specific promotion of lipid efflux from astrocytes and neurons in culture. J Neurochem 2000;74(3):1008–1016. [PubMed: 10693931]
150. Mahley RW, Huang Y, Rall SC Jr. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia). Questions, quandaries, and paradoxes. J Lipid Res 1999;40(11):1933–1949. [PubMed: 10552997]
151. Stratman NC, Castle CK, Taylor BM, Epps DE, Melchior GW, Carter DB. Isoform-specific interactions of human apolipoprotein E to an intermediate conformation of human Alzheimer amyloid-beta peptide. Chem Phys Lipids 2005;137(1–2):52–61. [PubMed: 16140289]
152. Buttini M, Orth M, Bellosta S, et al. Expression of human apolipoprotein E3 or E4 in the brains of Apoe−/− mice: isoform-specific effects on neurodegeneration. J Neurosci 1999;19(12):4867–4880. [PubMed: 10366621]

153. Keller JN, Lauderback CM, Butterfield DA, Kindy MS, Yu J, Markesbery WR. Amyloid beta-peptide effects on synaptosomes from apolipoprotein E-deficient mice. J Neurochem 2000;74(4): 1579–1586. [PubMed: 10737615]

154. LaDu MJ, Pederson TM, Frail DE, Reardon CA, Getz GS, Falduto MT. Purification of apolipoprotein E attenuates isoform-specific binding to beta-amyloid. J Biol Chem 1995;270(16): 9039–9042. [PubMed: 7721816]

155. Canevari L, Clark JB. Alzheimer's disease and cholesterol: the fat connection. Neurochem Res 2007;32(4–5):739–750. [PubMed: 17191138]

156. Pitas RE, Boyles JK, Lee SH, Foss D, Mahley RW. Astrocytes synthesize apolipoprotein E and metabolize apolipoprotein E-containing lipoproteins. Biochim Biophys Acta 1987;917(1):148–161. [PubMed: 3539206]

157. Uchihara T, Duyckaerts C, He Y, et al. ApoE immunoreactivity and microglial cells in Alzheimer's disease brain. Neurosci Lett 1995;195(1):5–8. [PubMed: 7478253]

158. Baskin F, Smith GM, Fosmire JA, Rosenberg RN. Altered apolipoprotein E secretion in cytokine treated human astrocyte cultures. J Neurol Sci 1997;148(1):15–18. [PubMed: 9125385]

159. Aoki K, Uchihara T, Nakamura A, Komori T, Arai N, Mizutani T. Expression of apolipoprotein E in ballooned neurons-comparative immunohistochemical study on neurodegenerative disorders and infarction. Acta Neuropathol 2003;106(5):436–440. [PubMed: 12898155]

160. Xu PT, Gilbert JR, Qiu HL, et al. Specific regional transcription of apolipoprotein E in human brain neurons. Am J Pathol 1999;154(2):601–611. [PubMed: 10027417]

161. Boschert U, Merlo-Pich E, Higgins G, Roses AD, Catsicas S. Apolipoprotein E expression by neurons surviving excitotoxic stress. Neurobiol Dis 1999;6(6):508–514. [PubMed: 10600406]

162. Ignatius MJ, Gebicke-Härter PJ, Skene JH, et al. Expression of apolipoprotein E during nerve degeneration and regeneration. Proc Natl Acad Sci U S A 1986;83(4):1125–1129. [PubMed: 2419900]

163. Nagy Z, Esiri MM, Jobst KA, et al. Influence of the apolipoprotein E genotype on amyloid deposition and neurofibrillary tangle formation in Alzheimer's disease. Neuroscience 1995;69(3): 757–761. [PubMed: 8596645]

164. Gibson GE, Haroutunian V, Zhang H, et al. Mitochondrial damage in Alzheimer's disease varies with apolipoprotein E genotype. Ann Neurol 2000;48(3):297–303. [PubMed: 10976635]

165. Blacker D, Haines JL, Rodes L, et al. ApoE-4 and age at onset of Alzheimer's disease: the NIMH genetics initiative. Neurology 1997;48(1):139–147. [PubMed: 9008509]

166. Martins CA, Oulhaj A, de Jager CA, Williams JH. APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. Neurology 2005;65(12):1888–1893. [PubMed: 16380608]

167. Green RC, Cupples LA, Go R, et al. Risk of dementia among white and African American relatives of patients with Alzheimer disease. JAMA 2002;287(3):329–336. [PubMed: 11790212]

168. Romas SN, Santana V, Williamson J, et al. Familial Alzheimer disease among Caribbean Hispanics: a reexamination of its association with APOE. Arch Neurol 2002;59(1):87–91. [PubMed: 11790235]

169. Payami H, Zareparsi S, Montee KR, et al. Gender difference in apolipoprotein E-associated risk for familial Alzheimer disease: a possible clue to the higher incidence of Alzheimer disease in women. Am J Hum Genet 1996;58(4):803–811. [PubMed: 8644745]

170. Breitner JC, Wyse BW, Anthony JC, et al. APOE-epsilon4 count predicts age when prevalence of AD increases, then declines: the Cache County Study. Neurology 1999;53(2):321–331. [PubMed: 10430421]

171. Mayeux R, Saunders AM, Shea 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(8):506–511. [PubMed: 9468467]

172. Silverman JM, Ciresi G, Smith CJ, et al. Patterns of risk in first-degree relatives of patients with Alzheimer's disease. Arch Gen Psychiatry 1994;51(7):577–586. [PubMed: 8031231]

173. Jayadev S, Steinbart EJ, Chi YY, Kukull WA, Schellenberg GD, Bird TD. Conjugal Alzheimer disease: risk in children when both parents have Alzheimer disease. Arch Neurol 2008;65(3): 373–378. [PubMed: 18332250]

174. Tsuang D, Larson EB, Bowen J, et al. The utility of apolipoprotein E genotyping in the diagnosis of Alzheimer disease in a community-based case series. Arch Neurol 1999;56(12):1489–1495. [PubMed: 10593304]

175. van der Cammen TJ, Croes EA, Dermaut B, et al. Genetic testing has no place as a routine diagnostic test in sporadic and familial cases of Alzheimer's disease. J Am Geriatr Soc 2004;52(12):2110–2113. [PubMed: 15571552]

176. Levy-Lahad E, Tsuang D, Bird TD. Recent advances in the genetics of Alzheimer's disease. J Geriatr Psychiatry Neurol 1998;11(2):42–54. [PubMed: 9877525]

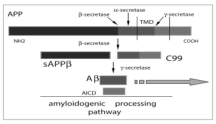

Figure 1.

Amyloidogenic processing of the amyloid precursor protein (APP) and generation of the β-amyloid peptides. The APP protein can be cleaved by 3 different secretases: α, β, or γ. Subsequent to "normal" α-secretase cleavage, sAPPα is produced and released into the extracellular space and the C83 peptide remains in the cell membrane (panel B). Subsequent to β-secretase cleavage, sAPPβ is produced and released into the extracellular space and the C99 peptide remains in the cell membrane Subsequent to β-secretase cleavage, the C99 peptide is "abnormally" cleaved by γ-secretase to yield an Aβ peptide and the AICD peptide. Scale is approximate. Aβ indicates amyloid-β peptide; AICD, amyloid precursor protein intracellular domain; sAPPβ, soluble fragment amyloid-β peptide; TMD, transmembrane domain. Large arrow represents accumulation of plaques or amyloid plaque deposition.

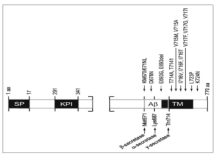

Figure 2.
Amyloid precursor protein (*APP*) structure and mutations. Thus far, over 32 different *APP* missense mutations have been identified, of which a few are shown. SP indicates signal peptide; KPI, Kunitz protease inhibitor domain; Aβ, amyloid-β; TM, transmembrane domain. Scale is approximate.

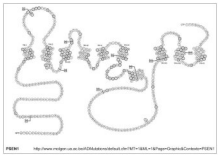

Figure 3.
Presenilin 1 (*PSEN1*) structure and mutations. Thus far, there have been at least 123 mutations in the *PSEN1* gene described, of which a few are shown. For a more complete list of *PSEN1* mutations, see http://www.molgen.ua.ac.be/ADMutations. TM indicates transmembrane domains. Scale is approximate.

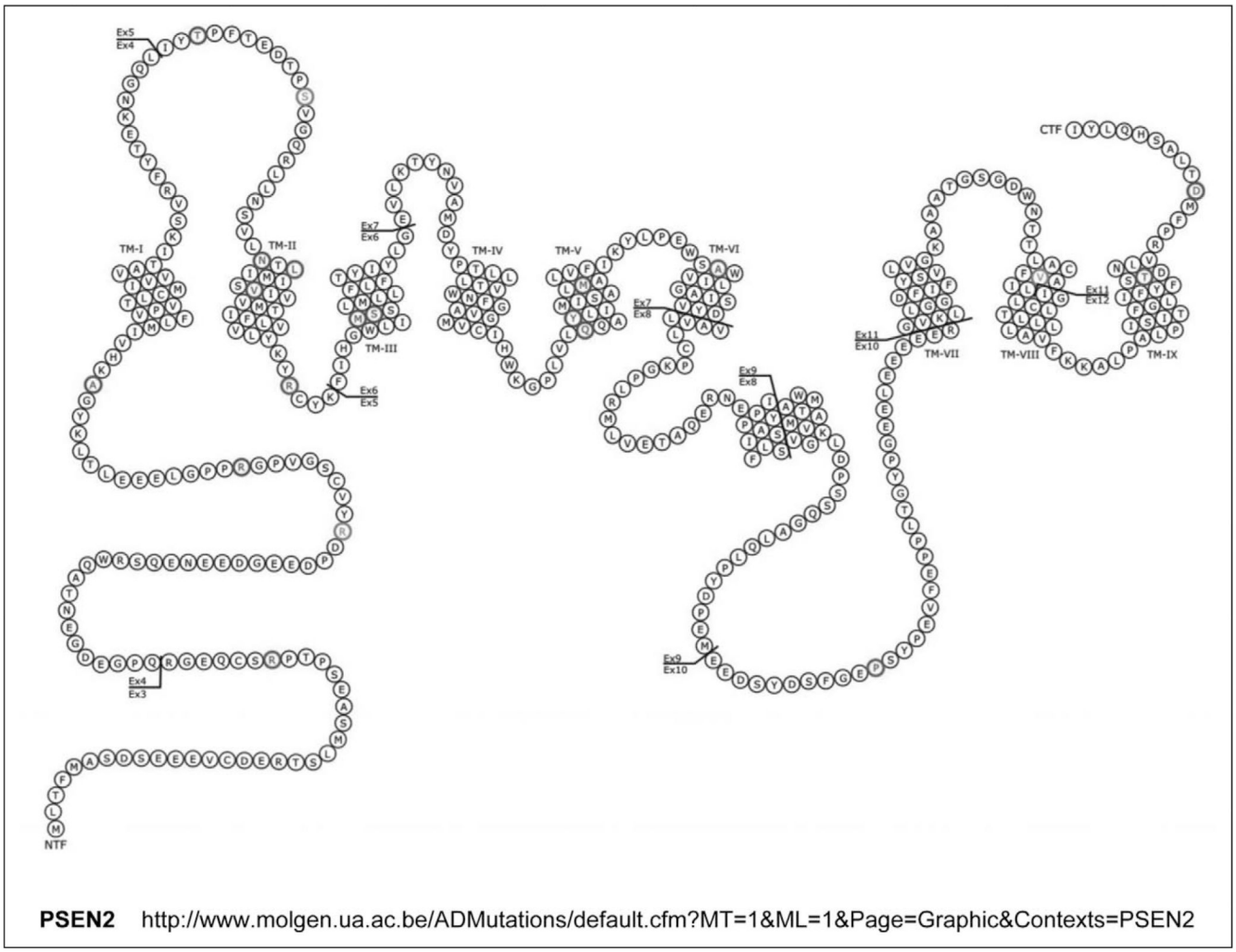

Figure 4.

Presenilin 2 (*PSEN2*) structure and mutations. Thus far, there have been at least 16 mutations in the *PSEN2* gene described, of which a few are shown. For a more complete list of *PSEN2* mutations, see http://www.molgen.ua.ac.be/ADMutations. TM indicates transmembrane domains. The V393M novel mutation was most recently found in 1 case (Lindquist et al).[126] Scale is approximate.

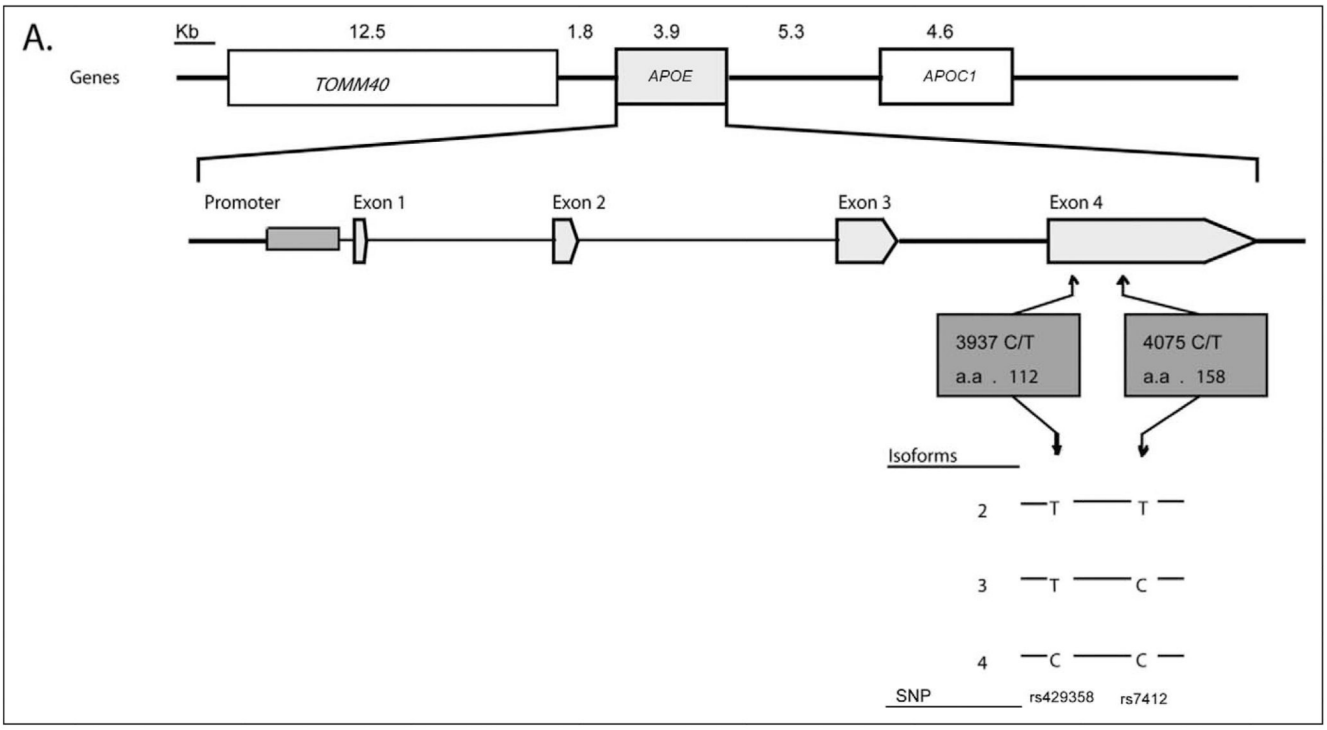

Figure 5.

Apolipoprotein E (*APOE*) structure and single nucleotide polymorphisms (SNPs). The general protein structure of *APOE* is shown. The 2 SNPs in exon 4 and corresponding protein locations are shown (rs429358 and C112R; and rs7412 and R158C). The 3 APOE ε4 alleles (ε2, ε3, and ε4) are defined by 2 SNPs, rs429358 and rs7412, with ε2 defined by nucleotides T-T; ε3 defined by T-C, and ε4 defined by C-C, respectively.

Table 1

Alzheimer Disease (AD) Genes[a]

AD Loci	Gene Symbol	Gene Name	Chromosome	Inheritance
AD1	*APP*	Amyloid precursor protein	21q21	Autosomal Dominant
AD2	*APOE*	Apolipoprotein E	19q13.32	Sporadic
AD3	*PSEN1*	Presenilin 1	14q24.2	Autosomal Dominant
AD4	*PSEN2*	Presenilin 2	1q42.13	Autosomal Dominant

[a] Alzheimer disease genes are located on 4 different chromosomes and are associated with autosomal dominant or sporadic inheritance.