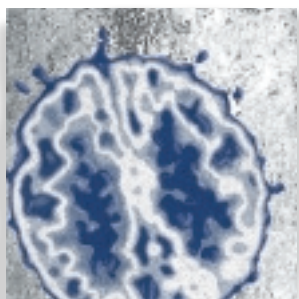# Basic research

Genetic studies in Alzheimer's disease
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Alzheimer's disease (AD), the most common cause of dementia in aged populations, is believed to be caused by both environmental factors and genetic variations. Extensive linkage and association studies have established that a broad range of loci are associated with AD, including both causative and susceptibility (risk factor) genes. So far, at least three genes, APP, PS1, and PS2, have been identified as causative genes. Mutations in these genes have been found to cause mainly early-onset AD. On the other hand, APOE has been identified to be the most common high genetic risk factor for late-onset AD. Polymorphisms in the coding region, intron, and promoter region of certain genes constitute another kind of genetic variation associated with AD. A number of other genes or loci have been reported to have linkage with AD, but many show only a weak linkage or the results are not well reproduced. Currently, the measurable genetic associations account for about 50% of the population risk for AD. It is believed that more new loci will be found to associate with AD, either as causative genes or genetic risk factors, and that eventually the understanding of genetic factors in the pathogenesis of AD will be important for our efforts to cure this illness.

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In 1907, Alois Alzheimer, a Bavarian psychiatrist, reported the case of a middle-aged woman who developed progressive memory loss and cognitive disorders with autopsy findings of neuritic plaque and neurofibrillary tangles in the cerebral cortex.[1] Thereafter, it was named as Alzheimer's disease (AD). However, it was only in the 1960s that came to be recognized as the most common cause of dementia in the aged.[2] AD currently accounts for at least 60% to 70% of cases of dementia in aged people.[3] In the United States, the total prevalence of AD is greater than 2.3 million and potentially affects more than 4 million individuals.[4] The average duration of AD is 8 to 10 years, or even shorter. AD has been ranked as the fourth leading cause of death in the United States.[2] By the year 2025, over 22 million patients with dementia are expected around the world.[5,6]

Pathology of AD

The pathologic criteria for diagnosis of AD require the presence of both neuritic plaques and neurofibrillary tangles, together with a progressive decline in cognitive function.[7] The neuritic plaques are composed of aggregations of β-amyloid (Aβ) and are surrounded by dystrophic neurons and astrocytes.[8-10] The neurofibrillary tangles consist of intraneuronal aggregations of hyperphosphorylation microtubule–associated protein tau.[11-14] Reduction in synaptic density and neuronal loss in some specific brain regions, including the cerebral cortex and hippocampus, are also important criteria in the diagnosis of AD.[15-19] Clinically, AD is rarely found in people under the age of

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65. In patients under this age, it is called early-onset AD, and if an obvious familial history can be traced, it is called familial AD (FAD). The youngest reported case of AD was found in a 25-year-old person.[6] In patients with age of onset over 65 years, it is called late-onset AD. The majority of the cases of AD are late-onset.[3,20] AD in patients without any family history of the disease is called sporadic AD (SAD). The etiology of AD is not clear. One critical demographic factor is aging. The prevalence of AD doubles every 5 years after age 60 from less than 1% prevalence between 60 and 64 years old to more than 40% in those aged 85 years or older.[21,22] Although environmental factors, such as education, head trauma, and diet, are thought to be involved in the pathogenesis of AD, no consistent findings have been reported.[23-26] The other demonstrated risk factor is genetic variation.[27,28]

Genetic factors

The first direct evidence of the significant implication of genetic factors in the pathogenesis of AD came from epidemiological studies. AD aggregates within families[29,30]: first-degree relatives of AD patients have a 3.5 times greater risk of developing the disease than the general population. Concordance rates were found to be 35% in dizygotic twins and as high as 80% in monozygotic twins.[31,32] In particular, many early-onset AD cases exhibit an autosomal dominant pattern of inheritance.[5,32-34] In addition, there is a significant association between AD and Down's syndrome.[35] However, the involvement of genetics in the pathogenesis of AD is very complicated.

First, as stated above, in some cases AD is an autosomal dominant inherited disease. Single gene mutation is sufficient to cause the disease. However, it is different from many typical inherited diseases with single gene mutation, such as Huntington's disease, because it shows true genetic heterogeneity.[36] In autosomal dominant inheritance AD, mutations in at least three different genes are each sufficient to produce the illness. In addition, variants of these genes have synergistic effects on the development of late-onset AD.[17,37,38] Second, the autosomal dominant inherited types of AD identified so far do not account for the majority of cases of AD (only about 5% to 10% of all cases).[17,20,32] However, it has been shown epidemiologically that more than 50% (or even up to 80%) of cases of AD have a genetic determination in a nonmendelian pattern, possibly as an incompletely penetrant trait. It is has been shown that certain genetic variations predispose to AD, but do not invariably cause AD (see below). Third, the fact that the incidence of AD closely correlates with aging suggests a significant contribution of environmental factors to the pathogenesis.[2,39] However, the similarities between early-onset and late-onset AD in terms of clinical and pathophysiological manifestations suggest a dominant role for genetic factors in the determination of the phenotypes of all cases of AD.[17,40] All these observations indicate that AD is a very complex disease genetically.[6,17,20]

Amyloid precursor protein

The first single gene that was found to cause AD was the gene for amyloid precursor protein (APP) on chromosome 21. Following linkage analysis, a mutation in *APP* was observed in FAD,[41,42] and was later identified as a mutation at codon 396 (Glu693Gln).[43] Thereafter, more than 16 other *APP* mutations were reported in 40 families around the world. The most frequently observed *APP* mutation is the London mutation (Val717Ile), which has been observed in 23 families of various ethnic origins.[44-47] There are three other kinds of mutations at codon 717: Val717Leu, Val717Phe, and Val717Gly. The second most frequent mutation is a Dutch mutation (Glu693Gln), which has been seen in four families.[43] Other reports include a Swedish mutation at codon 670/671,[48] a Flemish mutation at codon 692,[49] and others. *APP* mutations can result in both FAD and SAD, but the majority of AD cases caused by *APP* mutations are FAD.[6,50] Not all *APP* mutations are pathogenic.[6,17,51] It has been estimated that the AD caused by *APP* mutations accounts for only about 0.5% of all cases of AD.[32]

The current hypothesis about the role of *APP* in AD is the amyloid cascade theory.[52-54] The principle of this theory is that certain Aβ peptides (which are derived from APP) are neurotoxic, and that the accumulation of these peptides in the brain is the central event for triggering the

pathoanatomical and pathophysiological changes in the brain of AD patients, including the formation of neuritic plaques and neuronal loss. The finding of *APP* mutations in AD dramatically strengthened this hypothesis. The *APP* gene encodes for a transmembrane protein containing 770 amino acids, which is extensively expressed on the cell surface.[34,55,56] The function of APP is not yet clearly understood. It is generally considered that APP undergoes a series of endoproteolytic cleavages during its processing.[53,57] Three kinds of cleavage events are involved, α, β, and γ cleavage: α cleavage cleaves Lys687 and Leu688 to generate Aβ peptides with 16 to 17 amino acids (Aβ16 and Aβ17), while β cleavage cleaves Met671 and Asp672 to generate Aβ40 to Aβ42.[58] Aβ40 is the dominant product of the normal cleavage of APP and is found in the normal aged brain.[51,59-61] In contrast, γ cleavage cleaves Ile712, Thr714, or Val715 to generate Aβ40, Aβ42, and Aβ43, respectively,[62,63] and the latter two forms are the major components of the neuritic plaques observed in the AD brain.[51,54,64,65] Since they are more fibrillogenic and neurotoxic than Aβ40, Aβ42 and Aβ43 are currently considered to play a central role in the pathological processes of AD.[66,67] Therefore, enhancement of γ cleavage is thought to be a primary reason for why mutant *APP* causes AD. It has been shown that most of the *APP* mutations found in AD are located in the molecular region around the secretase sites, suggesting that these mutations lead to changes in the substrate in proteolytic processing. Indeed, it has been found that many *APP* mutations in AD significantly enhance APP cleavage, especially γ cleavage.[63,65,68-72] All these findings suggest that Aβ metabolism is a key pathway and should be targeted for therapy. Indeed, a compound that can inhibit γ cleavage of APP, a small molecule that can bind to Aβ to prevent its deposition, or an anti-inflammatory agent that can diminish the toxic response associated with Aβ have been the major focuses of our attempts to cure this illness.[17] Recently, transgenic mice that have a known AD-causing human mutation have been immunized with synthetic human Aβ peptide; this led to a significant reduction in the pathological changes associated with the mutant *APP* and a better performance.[10,12] This could be a novel therapeutic strategy to target Aβ neurotoxicity in AD.

Presenilin

APP mutations result in only a small proportion of autosomal dominant inherited types of AD, which is why there have been so many linkage studies of other loci with FAD. The observation of linkage with chromosomal region 14q in some FAD families eventually led to the discovery of a novel gene, namely presenilin 1 (*PS1*).[73-76] The first *PS1* mutation associated with FAD was reported in 1995.[73,77,78] Since then about 120 kinds of *PS1* mutation have been reported in about 260 families around the world. Almost all of the reported *PS1* mutations are missense and give rise to the substitution of a single amino acid. So far, only two splicing defect mutations have been reported[79,82]; these change the topography of the protein in membranes. In addition, the mutations are most frequently observed in exon 5 (28 mutations), exon 7 (23 mutations), and exon 8 (20 mutations). Mutation in the intron was also found to be able to produce AD.[83] Of the 120 *PS1* mutations reported, the majority were only found in a single AD family. The most frequently observed is the AD-associated *PS1* mutation on codon 206 (Gly206Ala), and was found in 18 families. The other common mutations are Met146Len in 12 families, Glu280Ala in 12 families, His163Arg in 10 families, and Pro264Leu in 8 families. Almost all of the *PS1* mutations were found to cause early-onset AD. However, *PS1* mutation on codon 318 (Glu318Gly) was found in 6 families with SAD and 4 families with FAD, and even in normal subjects.[84,85] Therefore, this mutation is called a partial pathogenetic factor.

The gene for presenilin 2 (*PS2*) was first identified on chromosome 1 in the public nucleotide sequence database, and has an overall 62% homology to *PS1*.[86,87] The first mutation in *PS2* found to associate with FAD was identified in a German family by linkage studies.[86,87] Thereafter, more than eight kinds of missense mutations in *PS2* were found to cause AD. However, the *PS2* mutations do not only produce FAD and late-onset AD.[74,88] There is one known case of a *PS2* mutation with apparent nonpenetrance in an asymptomatic octogenarian transmitter of the disease.[74]

Currently, most researchers believe that the major pathological role for mutant *PS1* and *PS2* in AD comes from their capacity to facilitate production of amyloidogenic Aβ42 peptides.[67,89] This "gain-of-function" hypothesis has been evidenced by many biochemical findings and transgenic studies.[89,90] Presenilin is a conserved polytopic membrane–spanning protein family consisting of PS1, a 463–amino acid polypeptide, and PS2, a 448–amino acid polypeptide.[75,86,91] Immunohistochemical analyses indicate that both PS1 and PS2 are

widely expressed in the brain, both in neurons and in glia, and with the highest levels in the pyramidal neurons of the hippocampus.[86,92-95] Biochemical studies have shown that PS1 and PS2 both have eight membrane-spanning segments with a large hydrophilic loop between the transmembrane domains 6 and 7, and the N-terminal and C-terminal both face the cytoplasm.[96-100] This unique structure confers their capacity to interact with other cytoplasmic proteins. Both of these hypotheses have been supported experimentally: γ-secretase is an oligomeric complex containing presenilin[91,101-105]; and presenilin itself acts as a γ-secretase.[103,106-110] Indeed, compelling evidence has emerged to support a role for *PS1* and *PS2* in the γ-secretase proteolysis of APP, Notch (a transmembrane protein essential for neurogenesis), and other substrates.[105,107,109,111-116] For example, *PS1* facilitates the proteolysis of APP C-terminal fragments by α- and β-secretase,[106,109,116-119] which produces Aβ peptides, including Aβ42.[84,89,120] Loss of presenilin function results in diminished Aβ production.[109,121-123] The *PS1* or *PS2* mutations found in AD do not result in loss of function.[111,120,121,124,125] Instead, these missense mutants significantly and specifically enhance γ-secretase cleavage to generate amyloidogenic Aβ42 peptides.[69,89,90,126,127] All these findings point to a central role for *PS1* and *PS2* in both APP processing and AD pathogenesis. However, a critical question here is why so many different kinds of mutation in either *PS1* or *PS2* produce gain of function to enhance γ-cleavage. Recently, it has been reported that polymorphisms in *PS1* and *PS2* increase risk of developing late-onset AD.[128] The pathway by which these polymorphisms predispose to AD is not clear.

These findings make it extremely difficult to understand the role of presenilin-regulated APP metabolism in the pathogenesis of AD. Moreover, we have recently found that *PS1* plays an important role in adult neurogenesis in the brain.[129] On the basis of the fact that neuronal loss in the brain is a hallmark of AD, it is possible that the loss of function associated with presenilin mutations, and hence neurogenesis, is another molecular pathway by which presenilin mutation leads to AD.

It should be noted that, although *PS1* mutations are more common in FAD, the *PS1* and *PS2* mutations combined are only implicated in about 8% of cases of early-onset FAD.[32,130-132] The majority of AD is late-onset, and the determination of the contribution of genetic variations in these patients is fundamental to our understanding of the pathogenesis of AD.

Apolipoprotein E

Apolipoprotein E (APOE) was originally reported as a risk factor for cardiovascular disease. First, a weak linkage was found between a locus of chromosomal region 19q and FAD,[133] and then a stronger association between *APOE* and late-onset AD was reported in 1993.[134] This linkage has been well reproduced in subsequent association studies and it is now established that *APOE* is the most common genetic risk factor for late-onset AD,[133-139] though it appears that there are additional common susceptibility genes associated with late-onset AD.[38,40,135,140,141] The *APOE* gene in humans contains three main polymorphisms, ε2, ε3, and ε4, of which ε3 is the most common (75%). The ε3 polymorphism contains a cysteine at codon 112 and an arginine at codon 158. The ε4 polymorphism represents an arginine at codon 112 and was found to strongly associate with late-onset AD.[133,139] Persons homozygous for ε4 have almost a 15-fold higher risk of developing AD, and persons heterozygous for ε4 have a 3-fold higher risk than those who do not carry this allele.[142,143] This dose–response relationship provides a strong argument for the *APOE* polymorphism being a contributing factor for AD. The ε2 polymorphism contains a cysteine at codons 112 and 158, and has also been found to associate with late-onset AD.[134] In addition, it has been reported that the ε4 polymorphism or a polymorphism in the promoter region is associated with early-onset AD.[135,144] Furthermore, polymorphisms within the promoter regions of the APOE gene, such as the region at 491 amino acids upstream of the *APOE* transcriptional start site (-491 A/T), were also found to associate with AD.[145-148] It has been shown that these polymorphisms (ie, at -491 A/T and at the ε4 allele) are independent genetic risk factors.[37] A study of 5.5 kb of the *APOE* gene found at least 22 single nucleotide polymorphisms (SNPs). These SNPs generate 31 distinct haplotypes and 7 SNPs were found in promoter region.[149] A role for these polymorphisms in pathogenesis of AD has not been shown.[40]

Despite these robust association results, there are still conflicting reports. A major discrepant finding came from studies in African-American and Hispanic populations, which did not find any association of the ε4 allele with AD.[150-152] Also, it is not clear why some homozygotes of ε4 still do not show any obvious AD symptoms, even when they are in their nineties. On the other hand, most AD patients do not harbor an ε4 allele.[17] In addition, some studies indicate no increased risk factor for AD with

the promoter (-491 A/T) genotype in Caucasian,[153] Japanese,[67,154] or Chinese[155] populations. It is reasonable to consider that the *APOE* polymorphism is only a genetic risk factor, but not a causative gene. This is also evidenced by the finding that many other factors, such as head injury,[156,157] spontaneous intracerebral hemorrhage,[158] and heart surgery,[159] facilitate the association of *APOE* polymorphism with AD.

The mechanism by which the *APOE* gene is implicated in AD pathogenesis is still unclear. The current hypothesis is that *APOE* ε4/ε2 polymorphisms may affect the production, distribution, or clearance of Aβ. There is evidence to show that *APOE* genotype is a factor affecting the age of onset of AD with the London *APP* mutation, suggesting a direct biochemical interaction between APOE and Aβ.[160-162] However, an open question here is why this synergistic effect on age of onset is only observed for the London *APP* mutation, but not in other mutations such as the Flemish mutation.[5] Another line of evidence to support this hypothesis comes from the observations that a higher Aβ plaque burden was observed in AD patients with *APOE* ε4 allele than without *APOE* ε4 allele.[163-165] It has also been reported that APOE and Aβ may share the same clearance mechanism, which is through the lipoprotein-related receptor, and ε4 competes with Aβ for clearance by the receptor.[166] However, in many cases, changes in Aβ deposition are not significantly correlated with the presence of the *APOE* ε4 allele, which leads to an uncertain status for this hypothesis.[17] Other possible mechanisms for the involvement of *APOE* polymorphisms in AD pathogenesis include (i) the ε4/ε2 allele enhancing the formation of neurofibrillary tangles[167,168]; and (ii) the ε4 allele reducing the normal function of ε3 in maintaining normal synaptic density.[169,170] All these ideas remain hypothetical. Remarkably, the ε4/ε2 central theory in the *APOE* hypothesis is challenged by the findings of polymorphisms in promoter regions of *APOE* that are associated with AD independently of the ε4 allele.[37] This independence indicates that the presence of ε4/ε2 alleles is not the only factor implicating the involvement of *APOE* in the pathogenesis of AD, since it is supposed that the polymorphisms in the promoter region may alter level of expression of ε3, but not ε4.[145,147]

Other genetic risk factors

The mutations in *APP*, *PS1*, *PS2*, and *APOE* polymorphisms account for less than half of the genetic variance in AD, which indicates that there must be other susceptibility loci or genetic risk factors in this disease.[171,172] Indeed, on chromosome 12, at least three genes were found to associate with AD. One is α2-macroglobulin (*A2M*).[173,174] Like APOE, A2M is a ligand for a lipoprotein-related receptor, and its functions are related to the binding, degradation, and clearance of the Aβ that accumulates in senior plaques.[175] Two *A2M* polymorphisms were identified in association with AD,[173] and other positive associations with AD have been reported[176-180]; however, some negative associations have also been found.[181,182]

Another gene with a potential involvement in AD risk is low-density lipoprotein receptor–related protein (*LRP1*), as reported in a study of 128 AD families.[183] LRP1 is the receptor for Aβ clearance, which might share the same mechanisms as APOE or A2M. A detailed association study with a bigger sample size in different ethnic population is now required.

A third possible AD gene is synaptobrevin.[184] Synaptobrevin is a vesicle-associated membrane protein and its expression is associated with number of synapses. This is a good candidate gene since it can be used as an index for synaptic loss or neuronal loss,[184] which is a major observation in the AD brain.

On chromosome 10, associations between increased risk for AD and the loci D10S1423,[141,185,186] D10S1211,[141,187] and D10S1225[188,189] were reported. This variation needs to be studied further. The gene for insulin-degrading enzyme on chromosome 10 has also been associated with AD.[188,190] Since this gene has been shown to degrade Aβ in primary neuronal culture, it is a good candidate genetic risk factor for AD. Also, multiple regions on chromosome 9,[187,189] chromosome 6,[171,172] chromosome 1,[191,192] and chromosome 19[189] have been reported to associate with the risk for AD. Other genes reported to associate with AD include those for cathepsin D,[37] nerve growth factor (NGF),[137] FE65 (an adapter protein),[193] LBP-1c/CP2/LSF transcription factor,[193] bleomycin hydrolase,[193] α1-antichymotrypsin,[193] interleukin-1,[194,195] cyclooxygenase-2,[191,192,196] NOS-3 (NOS, nitric oxide synthase),[197] transferrin C2,[198] and many other genes.[37] However, the exact roles for these genes in the pathogenesis of AD are not yet clear, and some of these associations can be considered as insufficiently replicated. Nevertheless, they offer hope for progress in the identification of susceptibility genes, as well as for functional analysis of the associated gene products, which will further contribute to our understanding of AD pathogenesis.

Basic research

Conclusion

Linkage studies and association analysis are the two principal strategies of the last 20 years that have led to the identification of specific gene variants that contributing to the pathogenesis of AD. The overall conclusion from these studies is that the majority of AD is complex, is inherited in a nonmendelian pattern, and involves the interplay of susceptibility genes with environmental factors. Aging is still a crucial factor in the onset of this disease. Since the current genetic associations only account for about 50% of the population risk for AD, it is believed that more new loci will be disclosed to associate with AD, either as causative genes or as genetic risk factors. In the near future, we would expect linkage, association, and positional cloning studies with larger samples, and more sophisticated statistical, genomic, and proteomic analytical methods to further elucidate the genetic bases of AD. ❑

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Estudios genéticos en la Enfermedad de Alzheimer

La Enfermedad de Alzheimer (EA), la causa más común de demencia en poblaciones de senescentes, se cree que es causada tanto por factores ambientales como por variaciones genéticas. Extensos estudios de linkage y de asociación han establecido que una amplia gama de loci están asociados con la EA, incluyendo genes causales y de susceptibilidad (factor de riesgo). Hasta la fecha se han identificado al menos tres genes causales: APP, PS1 *y* PS2. *Se ha encontrado que mutaciones en estos genes causan principalmente EA de comienzo precoz. Por otra parte, se ha identificado a la APOE como el factor de alto riesgo genético más común para la EA de inicio tardío. Los polimorfismos en la región de codificación, en el intrón y en la región promotora de ciertos genes constituyen otra clase de variación genética asociada con la EA. Se ha reportado un número de otros genes o loci que tienen enlaces con la EA, pero muchos muestran sólo un enlace débil o los resultados no están bien reproducidos. Actualmente las asociaciones genéticas medibles dan cuenta de cerca del 50% de la población en riesgo para EA. Se piensa que se encontrarán más loci nuevos que se asocien con la EA, ya sea como genes causales o factores de riesgo genético, y que en un futuro la comprensión de los factores genéticos en la patogénesis de la EA será importante en nuestros esfuerzos para curar esta enfermedad.*

Études génétiques dans la maladie d'Alzheimer

L'association de facteurs environnementaux et de variations génétiques semble bien être à l'origine de la maladie d'Alzheimer (MA), cause la plus fréquente de démence chez les sujets âgés. Des études de liaison et d'association de grande envergure ont établi qu'un grand nombre de locus sont associés à la MA, y compris les gènes (facteurs de risque) de susceptibilité et les gènes causals. Jusqu'ici, au moins trois gènes, APP, PS1 *et* PS2 *ont été identifiés comme gènes causals. Les mutations de ces gènes sont responsables principalement de MA à début précoce. Par ailleurs,* APOE *a été identifié comme le facteur de risque génétique élevé le plus courant pour la MA à début tardif. Les polymorphismes de la région codante, l'intron, et la région activatrice de certains gènes constituent un autre type de variation génétique associé à la MA. Une relation entre plusieurs autres gènes ou locus et la MA a été rapportée mais, pour la plupart, le lien est faible ou bien les résultats sont mal reproduits. Actuellement, les associations génétiques mesurables expliquent environ 50 % des risques de la population pour la MA. Il est à prévoir que plusieurs autres nouveaux locus montreront une association à la MA, que ce soit comme gènes causals ou comme facteurs de risque génétique. Ainsi, la compréhension des facteurs génétiques dans la pathogenèse de la MA devrait contribuer de façon importante à nos efforts pour soigner cette maladie.*

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