Review

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Molecular mechanisms and genetics of Alzheimer's disease

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Abstract: Dementia is mostly caused by neurodegenerative diseases like Alzheimer's disease (AD). AD is the most common form of dementia. It is caused by both genetic and environmental factors. Due to neuronal death in a number of brain regions, including the hippocampus, entorhinal areas, temporal lobe, and cingulate cortex, AD causes memory loss and gradual cognitive impairment. The condition's two main pathogenic components are intracellular neurofibrillary tangles created by clusters of hyperphosphorylated tau protein and amyloid plaques made up of extracellular amyloid (Aβ) peptide aggregates. In contrast to the APOE- ε4 allele, which was found to have a significant impact on late-onset AD, presenilin 1, presenilin 2, amyloid precursor protein were genetic risk factors that were causal for early-onset AD. Misfolded proteins accumulate within the neuron, causing prolonged cellular stress in AD, a progressive neurodegenerative disease. Neurofibrillary tangles and senile plaques are two of the neuropathological hallmarks of Alzheimer's disease that lead to the destruction of synapses and the death of neurons. AD is mostly caused by the death of nerves, particularly cholinergic nerves. In the absence of these cholinergic neurons, acetylcholine levels fall. This review discusses key genes involved in the pathogenesis and pathophysiology of AD, as well as the disease's molecular mechanisms.

Keywords: Alzheimer's disease; apolipoprotein E; APP; neurodegenerative disease; pathogenesis; presenilins.

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Introduction

The economic and social toll of dementia care is staggering. Alzheimer's disease (AD) is the most frequent cause of dementia and other neurodegenerative and neurological disease [1]. More than two-thirds of all cases of dementia are diagnosed as having AD. Asymptomatic AD is caused by alterations in protein processing, signaling, inflammation, lipid transport, apoptosis, oxidative damage, stress responses, tau pathology, neurodegeneration, and energy metabolism that affect brain homeostasis. AD is marked by amyloid plaques and neurofibrillary tangles, which have been linked to a decline in brain function and memory loss [2]. Memory loss and a decline in cognitive functions that results in dementia are hallmarks of AD, the most common kind of neurodegenerative disease. Although their etiology is unclear, both extracellular and intracellular beta-amyloid plaques (Aβ) and hyperphosphorylated tau protein neurofibrillary tangles are clinically significant characteristics of AD [3].

Microdomains may arise from membrane-associated oxidative stress from extracellular Aβ aggregation near the cell membrane. In the early stages of Alzheimer's disease, the brains of people with the disease have more 4-hydroxynonenal (HNE), which is a neurotoxic aldehyde made by lipid peroxidation caused by oxidative stress on membranes. Neuronal damage was linked to elevated levels of HNE. Oxidative stress opens up the pathways linked to AD [4].

Amyloid precursor protein (APP), a crucial membrane protein, is broken down into Aβ peptides. The three main splice variants of the *APP* gene, APP695, APP751, and APP770, are generated in turn by neurons, endothelial cells, and platelets [5]. The most important biological risk factor is age, and the age of 65 is frequently used to divide AD patients into early-onset (EOAD) and late-onset (LOAD) categories. A diagnosis of EOAD affects about 10 % of all AD patients [6].

The most significant other unmodifiable risk factor for sporadic AD is apolipoprotein E (*APOE*) gene polymorphism (ϵ4 allele). Carrying one APOE ϵ4 allele raises the chance of getting AD threefold compared to ϵ3/ϵ3 persons, the most

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prevalent genotype in the general population, while possessing two APOE ϵ4 alleles increases the risk as much as twelvefold. Those who are homozygous for the APOE ϵ4 allele commonly show symptoms of AD well before the age of 65, and this effect is dose-dependent. Yet, carrying the APOE e2 allele halves the risk of Alzheimer's disease, delays its onset, and lowers neuropathological changes associated with aging [1].

Glial cells are now the main subject of study for Alzheimer's disease. In AD, microglia and astroglia assume numerous distinct states, which may explain their differential roles in pathology development and progression. There is evidence to support the idea that astroglia and microglia collaborate to cause illness. Astrocytes become reactive when activated by microglia and play important roles in the neuroinflammatory and neurodegenerative processes that occur in AD and other neurological illnesses [7]. In this review, the biochemical and histological differences in the pathology of AD and the molecular mechanisms of the disease are explained.

Etiology of Alzheimer's disease

Mutations in these presenilin genes, like those in the amyloid precursor protein genes, cause Alzheimer's disease to start early and probably work directly through the amyloidogenic pathway. Genetic risk factors are now thought to cause 80–90 % of sporadic Alzheimer's disease, unlike genetic mutations. AD may be caused by environmental factors, but no one has been able to say for sure. It is a complex disease with many possible causes [8]. Even though several risk and protective factors have been found, it is still not clear what causes AD. In addition to aging, family history and disposition are crucial risk factors. The prevalence of familial AD is 7–10 %; rare dominant early onset AD (EOAD) is caused by mutations of several genes: amyloid precursor protein *(APP)*, presenilin 1 *(PS1)*, presenilin 2 *(PS2)*, which enhance β-amyloid production from APP, while apolipoprotein E *(ApoE)* on chromosome 19 contributes to late-onset AD (LOAD) [9]. Both genetic and environmental factors may raise the risk of developing Alzheimer's disease. An important risk factor is age. AD is about 3 % more likely to occur at age 65, increasing to over 30 % at age 85. According to estimates, 3 % of AD cases develop under the age of 65, but the incidence is less certain [10].

Tau protein and Aβ peptide can be characterized and examined in AD lesions via histopathological analysis. The changes in tau protein and Aβ peptide over the past few years (amyloid cascade, tau hyperphosphorylation, mitochondrial cascade) suggest that the altered tau proteins and Aβ peptides contributed to the development of the disease, rather than causing it [11]. The basic etiology of Alzheimer disease is nerve destruction, particularly of cholinergic nerves. As a result of the destruction of these cholinergic nerves, there is a decrease in the level of acetylcholine in the brain. According to the current understanding of Alzheimer's vascular etiology, plaques and tangles are often observed in Alzheimer's patients [12]. In AD patients, missense mutations are at least four times more common than APP genomic duplications. Those with the APP mutation typically develop symptoms between the ages of 45 and 60. When compared to missense mutations, which show nearly 100 % disease penetrance, APP chromosomal duplications have a lower disease penetrance and a wider range of onset ages [6].

Epidemiology of Alzheimer's disease

According to projections made by the Center for Disease Control, the population of persons aged 65 and over is expected to grow from its current level of 420 million to come within striking distance of one billion by the year 2030. This expanding number of elderly people has imposed tremendous obligations not only on the economy of the whole world but also on the families and caregivers of individuals who are afflicted with age-related disorders. As the older population grows, AD may become a worldwide concern because of its relationship with aging. By 2050, nearly half of the 13.8 million Americans with AD dementia will be over the age of 85, according to projections from the Census Bureau. More than 36.5 million individuals across the globe are living with dementia right now, and the vast majority of these instances are due to Alzheimer's disease. Each year, between 5 and 7 million people over the age of 65 are diagnosed with Alzheimer's disease [13].

The most current Alzheimer's Association Facts and Figures Report stated that AD care cost 203 billion dollars in the preceding year, with Medicare paying 107 billion and Medicaid paying 35 billion. End-stage dementia patients are institutionalized, which drives this expense. An estimated 216 billion dollars in unpaid caregiver hours are lost annually due to the disease's intangible emotional effects [14]. AD seems to follow a normal distribution in terms of age and gender. Females have a two- to three-fold greater chance of developing any kind of dementia and Alzheimer's disease than males. Some additional research provides dementia and AD incidence rates in terms of the number of people per year. According to the findings of a prospective cohort study

conducted in the United Kingdom on 1,070 individuals aged 65 or older and followed for a period of three years, the incidence of dementia of any form was 9.2 per 1,000 in the population each year, with AD accounting for 6.3 per 1,000 [15].

The incidence of Alzheimer's disease and other forms of dementia is higher in women than in men. In Australia, for instance, women account for over 66 % of dementia-related deaths. It is not clear if this means that men in general have a higher death rate or just those with dementia and Alzheimer's disease. Recent findings imply that sporadic cases of Alzheimer's disease occur at roughly the same rates among people of different races and ethnicities living in different parts of the world. If this result holds up in future research, it will show that genes are more important than the environment [16].

Diagnosis

Alzheimer's disease diagnosis back in Alois Alzheimer's day was only possible through pathological means. A clinical strategy that relied on excluding criteria, however, replaced this approach in 1984. The International Working Group used a clinical and biological approach, and then the National Institute on Aging and the Alzheimer's Association used biomarkers to classify Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association's criteria. Dementia, a clinical disease characterized by severe progressive cognitive impairment impacting numerous domains or neurobehavioral symptoms of sufficient severity to create a noticeable functional effect on everyday living, was once required for an Alzheimer's disease diagnosis. Dementia is distinguished from moderate cognitive impairment by a loss of independence [17].

Memory loss is the hallmark characteristic of AD, which develops slowly. Nonetheless, patients can experience a wide range of symptom presentations. AD "variants" may appear with cognitive deficits in various areas and distinct cognitive profiles. Early abnormalities in episodic memory are a reflection of initial dysfunction in the medial temporal lobe and are shown in the most prevalent and "typical" form of amnestic presentation. When the disease progresses and the pathology extends to other parts of the body, people in the moderate-to-severe stages experience a worsening of their cognitive abilities and a growing inability to care for themselves [18].

CT or MRI should be used to find brain lesions or disorders, like tumors, subdural hematomas, or hydrocephalus, that may cause dementia syndromes or make them worse. Hence, it is safe to say that Alzheimer's disease is the cause of cognitive decline in the vast majority of cases, and scientific investigations can help rule out other significant causes of dementia. More precise biomarkers are required to enhance early Alzheimer's disease diagnosis. In cerebrospinal fluid, research has been done on the phosphorylation epitopes of the tau protein and the isoforms of the amyloid beta peptides. Meta-analyses reveal that lower $A\beta_{1-42}$ and greater total tau or tau hyperphosphorylated at threonine 231 and 181 concentrations than age-matched controls may distinguish Alzheimer's disease from other dementias [19].

When cerebrospinal fluid (CSF) biomarkers are used, there is more proof that mild cognitive impairment (MCI) is caused by AD. Nevertheless, categorization based on CSF biomarkers often yields contradictory profiles of uncertain prognostic significance. Using the Aβ42/40 ratio to normalize the amount of Aβ42 in CSF to the amount of total Aβ has been shown to help tell the difference between AD and other types of dementia [20]. Low amounts of Aβ42 and high concentrations of total tau (t-tau) and phosphorylated tau (p-tau) in CSF represent the pathophysiological characteristics of AD and have demonstrated great promise for symptomatic and presymptomatic AD assessment. CSF-AD biomarkers are used in studies of possible disease-modifying medications to select eligible individuals, track therapeutic target engagement, and assess clinical trial outcomes [21].

Recent data highlights a significant relationship between CSF biomarkers, including Aβ42, tau, and AD neuropathological alterations, and many studies attest to the efficacy of cerebrospinal fluid biomarkers in the diagnostic context of AD. The "AD signature" biomarker pattern shows reduced Aβ42 and elevated T-tau and phosphorylated-tau (P-tau181). Combining CSF Aβ42, T-tau, and P-tau181 increases diagnostic accuracy for distinguishing AD from non-AD dementia and predicting AD development in MCI patients. The Aβ42/Aβ40 ratio has also been shown to have a stronger correlation with amyloid plaques and imaging using the Aβ tracer in positron emission tomography (PET). This ratio minimizes usual intra- and inter-individual biological variability, increasing diagnostic performance, and allowing improved disease severity classification [22]. For research purposes, the CSF Aβ42/40 ratio may predict PET amyloid positivity with excellent accuracy in individuals with a variety of cognitive diseases. This is especially true when examining Aβ pathology independently of tau and neurodegeneration [23].

According to the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria, PET and fibrillar amyloid-binding radiopharmaceuticals (Amyloid-PET) can distinguish between markers of Aβ-deposition and

markers of neurodegenerative processes like atrophy on MRI, hypometabolism on ^{18}F-fluorodeoxyglucose PET imaging (FDG-PET), and increased levels of tau and p-tau proteins in the CSF. Nevertheless, the sensitivity of these tests is not as high as that of FDG-PET evaluation of the neuronal lesion, Amyloid-PET assessment of amyloid burden, or perfusion single-photon emission computed tomography of neuronal perfusion when it comes to early AD diagnosis (SPECT) [24]. PET can evaluate cognitive decline using either FDG or Aβ ligands, both of which are currently available for clinical use. The molecular specificity of amyloid PET for Aβ plaques (mostly neuritic and, to some degree, diffuse plaques) is essential for defining AD neuropathological alterations. FDG, which measures synaptic activity and neurodegeneration, indicates hypometabolism in the temporoparietal and posteromedial cortices in AD. FDG and amyloid-PET have both demonstrated high sensitivity for diagnosing AD neuropathology [25].

^{18}F-FDG-PET shows that people with dementia who have low metabolism in the brain have advanced neurodegeneration. ^{18}F-FDG-PET may find Alzheimer's disease neurodegenerative patterns earlier than MRI in people with moderate cognitive impairment who will get dementia. Amyloid-PET can find amyloid plaques, which are one of the most important neuropathological signs of Alzheimer's disease, in Alzheimer's patients who have had an autopsy within a year of PET imaging. With amyloid-PET, it is possible to find amyloid pathology even in Alzheimer's disease types that look different, like posterior cortical atrophy, the fronto-executive form, and the logopenic form. It cannot distinguish between amyloid-positive illnesses with comparable amyloid deposition patterns [26].

Alzheimer's disease pathophysiology

The pathological symptoms of AD, such as the emergence of Aβ, neurofibrillary tangle (NFT) and neuronal death, were first recognized by Alois Alzheimer in 1906 [27]. An accumulation of tau inclusions in neurons or glia is a hallmark of tauopathies. Tau pathology together with extracellular amyloid plaques define AD, a secondary tauopathy [28]. Neuritic plaques, which are microscopically located areas of extracellular amyloid deposition with accompanying axonal and dendritic damage, are one of two diagnostic brain lesions found in the first Alzheimer's disease patient. Aβ builds up outside of cells as amyloid fibrils, which come together to look like stars. This amyloid deposit and its surroundings have dystrophic neurites [29]. Although Aβ accumulation and NFT production are both believed to be crucial in the onset and progression of neurodegenerative illnesses like AD, their exact relationship to the etiology of AD is still highly contested [27]. Only neurons in AD are found to contain 3R and 4R Tau aggregates in the form of NFTs and neuropil threads. In AD, tau pathology occurs in six successive Braak phases that begin in the transentorhinal cortex and spread to the hippocampal and neocortex [28].

The disorder is characterized by cholinergic pathway atrophy and Aβ deposition. As well as the production of free radicals, N-methyl-D-aspartate receptor-mediated neurotoxicity, low levels of acetylcholine, amyloid depositions, and hyperphosphorylated tau proteins are the key pathogenic markers. Acetylcholine (ACh) neurotransmitter amounts are observed to be lower in the cholinergic observation, owing to increased activity of the acetylcholinesterase (AchE) enzyme and cholinergic atrophy. There is a decrease in ACh levels in the areas of the brain that function most crucially for memory: the cortex and the hippocampus [30]. Several factors may contribute to AD pathogenesis, including DNA methylation and small noncoding RNAs, especially miRNAs. Consequently, miRNA expression changes can induce translational repression, reducing protein levels. In several studies, miRNAs have been found to be causally linked to AD by affecting BACE1 and APP expression, affecting the underlying pathogenic pathways, thereby altering risk and progress [31].

As the condition progresses, laboratory tests including oxidative stress products, Aβ levels, oxysterols like 24- and 27-hydroxycholesterol, proinflammatory cytokines in blood and CSF should be done, along with neuroimaging examinations like MRI and PET. If neuropsychological tests show cognitive impairment, and biochemical and neuroimaging tests are positive, the diagnosis is "probable AD" or "possible AD." It is crucial to highlight that impairment in cognitive areas in which the clinical diagnosis is Alzheimer's disease corresponds, although not always, with the neuropathological aspects of postmortem brains with Alzheimer's disease. Nevertheless, this is not always the case. Pathological alterations, including hypometabolism, disruption of the blood-brain barrier, oxidative stress, mitochondrial dysfunction, and neuroinflammation, may be induced by various metabolic diseases that are regarded as substantial risk factors for AD. These changes are what distinguish AD from other forms of dementia. When microglia and astrocytes are activated, they make cytokines and reactive oxygen species that hurt neurons and cause Alzheimer's disease to get worse [32].

A molecular genetic approach to Alzheimer's disease

Most cases of early-onset familial AD are caused by autosomal dominant mutations, which affect only 2 %–5 % of all AD patients. Amyloid precursor protein, presenilin-1, and presenilin-2 are all candidates for carrying these mutations. Risk factor profiles and neuropathological characteristics vary widely in sporadic AD patients. Familial aggregation, which is caused by genetic and environmental factors, makes it more likely that first-degree relatives of Alzheimer's patients will also get the disease [33]. AD often comes in two different forms: sporadic and familial. The term "late-onset AD" is frequently used to describe sporadic AD, which affects adults beyond 65. The afflicted population ranges in age from 30 to 65, and it is known as EOAD. Inheritance and genetic variables have an influence on familial kinds of AD [34].

Aging is the primary essential genetic factor causing AD in old age, accounting for up to 90 % of AD individuals treated beyond the age of 65. Up to 82 % of people with LOAD may trace their diagnosis back to a genetic predisposition. As many as 90 % of cases of AD may be traced back to a familial origin among those who are diagnosed before the age of 65 [35]. Three genes, including APP, Presenilin 1, and Presenilin 2, have an uncommon autosomal dominant mutation that contributes to the familial type of AD [34].

Even though many genes and genetic pathways related to Alzheimer's disease have been found, a full understanding of the disease at the cellular and molecular levels has not yet been made. Unlike sporadic late-onset diseases with genetic variability and comorbidities, monogenic AD offers a fixed genetic starting point for disease causation research. Mutations bring autosomal dominant types of early-onset AD on in the genes encoding *PSEN1* and *APP* [36]. Aβ, especially Aβ42, is largely acknowledged as the principal cause of Alzheimer's disease; nevertheless, its mechanism is debatable. Since soluble Aβ is more directly linked to cognitive deterioration and synapse loss in AD brains than amyloid plaque density, it inhibits synaptic function [37].

Apolipoprotein E (ApoE)

ApoE is the late-onset gene that significantly increases amyloid plaque accumulation in AD brains, whereas the first three early-onset genes, *APP*, presenilin-1, and presenilin-2, are all genetically associated with the disease. ApoE is a polymorphic amino acid glycoprotein that has a molecular mass of 34,200 Da. There are three alleles of the same gene *(ApoE2, ApoE3, and ApoE4)* present at one gene locus in humans. These alleles give rise to all three isoforms. There is evidence that the ApoE ?4 allele is a major genetic risk factor for both late-onset and sporadic AD [38].

ApoE3 plays a neutral role in AD risk, while apoE2 is protective and apoE4 is detrimental. It has been shown that having more copies of the APOE ε4 allele makes you more likely to get Alzheimer's disease and speeds up its progress. Moreover, homozygosity for *apoE4* reduces the AD onset age from 84 to 68 years, demonstrating apoE4's role in AD pathogenesis. APOE ε4 contributes to hippocampal morphological deformation and accelerates cognitive decline as human aging progresses since it is associated with impaired memory. The interaction between ApoE4 and Aβ may enhance tau aggregation [39].

Recent research has discovered a complex polygenic risk factor for sporadic late-onset Alzheimer's disease. Researchers have found several additional genetic loci besides the ApoE polymorphism that are associated with the illness via genome-wide association analyses. The disease's intricate biological process involves several additional susceptibility genes. These loci provide polygenic risk scores for genetic risk profiles. The ability to modify polygenic risk scores would enable early identification and treatment of young people at risk of developing Alzheimer's disease [40].

It is also crucial to remember that the ApoE protein is made in the liver but is also produced in the brain and operates there in several ways, some of which may be related to AD. ApoE plays an important function in the brain, as it does everywhere in the body, in maintaining healthy levels of lipids and cholesterol. Hypolipidemia and decreased cholesterol efflux induction by ApoE4 compared to ApoE3 reveal that lipid metabolism is at the root of ApoE4's deleterious consequences [41].

Alzheimer's disease is characterized by NFTs. Phosphorylated tau (pTau) is the main component of NFTs. Tau stabilizes microtubules and aids axonal transport in the healthy brain. It has been shown that pTau buildup contributes to synaptic dysfunction, neurodegeneration, and eventually dementia. Finding out which proteins pathogenic pTau in Alzheimer's disease interacts with will help us understand how it contributes to the disease's cause and may lead to new therapeutic targets [42].

The amyloid precursor protein (APP)

Genetic, biochemical, and behavioral studies have shown that the physiologic synthesis of the neurotoxic Aβ peptide, which comes from the successive proteolysis of APP, is the

most important step in the progression of AD. The APP is a type of single-pass transmembrane protein that is digested by a number of proteases, one of which is the intramembranous γ-secretase complex [43]. APP synthesizes a type 1 transmembrane glycoprotein, which is digested whether through a nonamyloidogenic or amyloidogenic pathway. An amyloidogenic pathway or a nonamyloidogenic pathway can be used to separate the type 1 transmembrane glycoprotein that is produced by APP. The transmembrane domain of APP contains an extra 14 residues, bringing the total number of amino acids in APP to 770. Of these, 28 residues are found in Aβ [44].

As APP interacts with laminin and collagen and co-localizes with integrins, especially at cell adhesion sites like neural axons, it has been hypothesized that it plays a role in cell adhesion. Moreover, APP was demonstrated to promote cell expansion. Genetic elimination of APP in fibroblasts resulted in stunted cell proliferation and development. The recovery of sAPP levels recovered the effect. Copper and zinc-binding domains, collagen, laminin, heparin, and a protease inhibitor domain are all found in APP [45].

The action of γ-secretase results in complex, permeable, and hazardous Aβ fragments, which are synthesized by presenilin, nicastrin, presenilin-2, anterior pharynx defective 1. β-secretase cleaves the majority of the extracellular part of the protein to preserve the C-terminus of APP. This causes the C-terminus of A to form highly cleaved A oligomers, which cluster into plaques and strongly polymerize (Figure 1) [44].

A cascade of endoproteolytic cleavages occurs in the βAPP precursor protein. The extracellular N-terminus of APP is released by cleaving the βAPP695 peptide in the center of the Aβ peptide domain, a process that is thought to be carried out by a putative membrane-associated α-secretase. The alternate cleavage process comprises consecutive cleavages by β- and γ-secretases, resulting in the 40–42 amino acid Aβ peptide. The first cleavage in the Aβ domain is catalyzed by β-secretase, a type 1 transmembrane glycosylated aspartyl protease found on the cell surface and in post-Golgi membranes. The second series of cleavages is caused by γ-secretase, a putative enzyme activity found at residues +40 and +42 [46].

Presenilins [presenilin 1 (PS1) and presenilin 2 (PS2)]

By facilitating the intramembranous cleavage of APP and the production of Aβ, the presenilin (PS) proteins play a critical role in the pathogenesis of AD. *PS1* and *PS2* are catalytic subunits of two distinct -secretase complexes that regulate membrane protein metabolism, signal transmission, and cell differentiation. The intramembranous cleavage of selected proteins by γ-secretase regulates intracellular signaling pathways; however, the large number of protein substrates suggests that these enzyme complexes also regulate membrane protein homeostasis [47].

PS1 and *PS2* genes, found on chromosomes 14 and 1, cause autosomal dominant EOAD. Even though *PS2* and *PS1* share 67 % of their sequence, their N-termini and water-loving parts are different. The *PS2* gene has fewer than 40 mutations, whereas the *PS1* gene has over 200 mutations [48]. A family form of Alzheimer's disease (FAD) is caused by mutations in the *PS1* and *PS2* genes. PS2 variants display less penetrance than PS1 variants, with the average age at symptom onset for PS2 FAD mutations exceeding 10 years

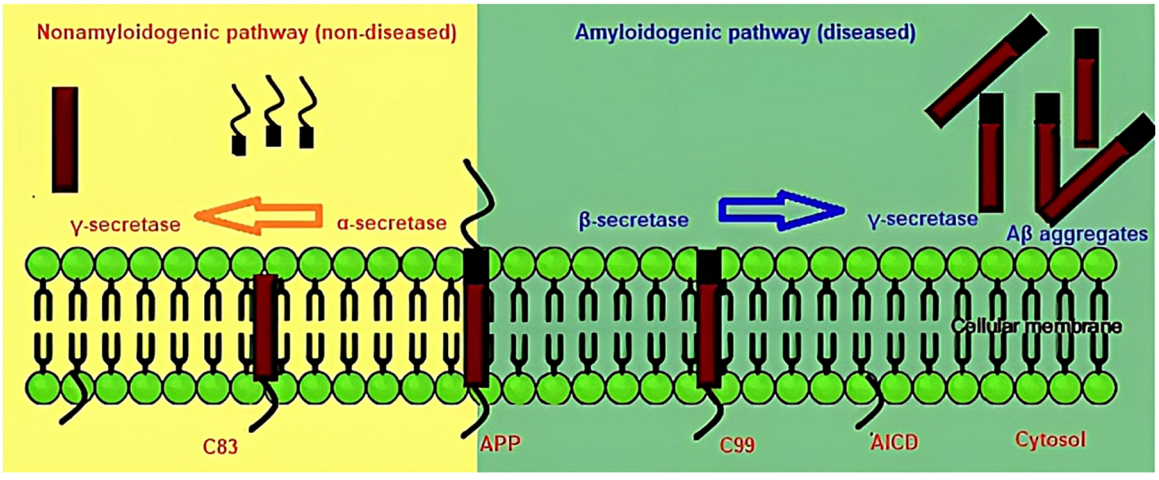


Figure 1: APP allows alternate splicing in routes that are amyloidogenic and non-amyloidogenic. With permission from ref. [44].

after PS1 mutations [49]. The 12 exons of the PS1 gene, the first two of which are 5′ untranslated regions, are structured across a length of more than 50–75 kb. The N-termini and the sixth hydrophilic loop of PS1 and PS2 are the main areas of difference between the two proteins; the rest of the amino acid sequences are quite similar (67 % identity). The PS1 missense mutations that are most common occur in their shared amino acids. A 24-kb genomic area is represented by 12 exons in PS2's gene structure, which is remarkably similar to that of PS1's [50].

In the γ-secretase complex, PS1 and PS2, two related 8-domain transmembrane proteins, catalyze the final phase of the APP cleavage to produce the peptides Aβ40 and Aβ42. The amino acid sequences of PS1's six alternative splicing variants are 184, 374, 378, 409, 463, and 467. PS-2 isoforms with 414 and 448 amino acids are identified. There are 144 missense mutations in PS1, only two of which are harmful (Figure 2) [51].

In comparison to wild-type γ-secretase, six FAD mutants in PS1 and five in the Aβ peptide section of the APP were studied, and all were found to be associated with lower γ-secretase activity, an earlier age at disease onset, and mortality. PS2 K115Efx10 causes PS2 protein truncation and is similar to a PS2 isoform, PS2V, which is present in the brains of people with late-onset AD. PS2V mutations also activated γ-secretase, lowering the unfolded protein response in hypoxia. Increases in the A42:A40 ratio have been linked to the etiology of AD, indicating that competitive γ-secretase inhibitors may be useful therapies for the disease. PS1 and PS2 both contain a conserved AXXAXXXG motif, which has been linked to the transition of normal and pathological γ-secretase conformations [52].

Genetic tests used in AD

Rare gene mutations have been linked to inherited forms of AD. The APOE gene and others like it serve as risk factors for late-onset sporadic AD. Patients with a family history of early-onset dementia and clinical symptoms suggesting AD may be examined for presenilin and amyloid precursor protein gene variants with pre- and post-test counseling [53]. Apolipoprotein E is a genetic marker that predicts Alzheimer's disease and long-term care needs. Those who learn they have the Alzheimer's-risking variation of a particular trait are more likely to purchase long-term care insurance [54]. Genetic tests that detect genetic risks associated with the APP, PS1, PS2, and APOE genes for Alzheimer's disease are given in Table 1.

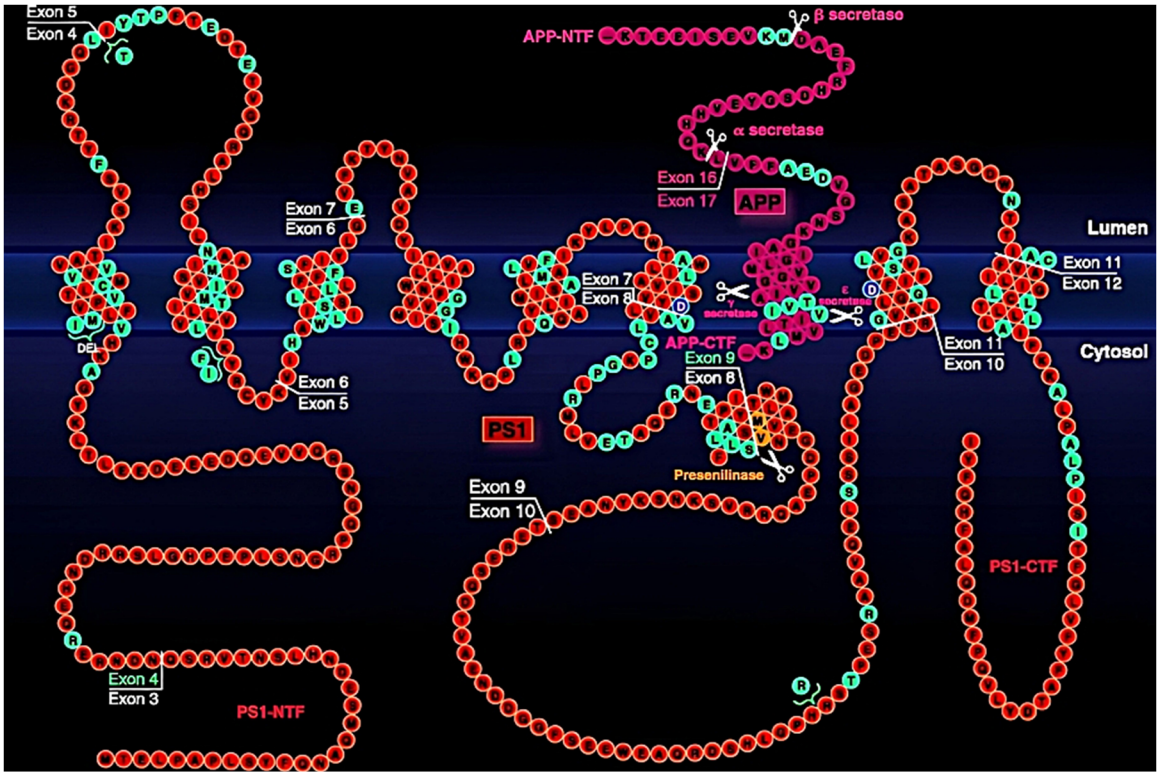


Figure 2: Aβ is produced by the PS1 amino acid sequence and the C-terminal region of the APP. [CTF, C-terminal PS-1 segment; NTF, N-terminal PS1 segment]. With permission from ref. [51].

Table 1: Genetic testing for APP, PS1, PS2, and APOE genes in Alzheimer's disease.

Genes	Genetic tests applied	Obtained results	References
ApoE	Real-time PCR using TaqMan-BHQ probes	Real-time PCR with TaqMan-BHQ probes for APOE genotyping matched up perfectly with data from DNA sequencing, which shows that the protocol is reliable. Genetically randomized cases and controls were in Hardy-Weinberg equilibrium ($p>0.05$). Cases and controls had very different distributions of APOE genotypes. The APOE 4 allele is a risk factor for late-onset AD due to its association with an increased likelihood of getting the condition.	[55]
	Enzyme-linked immunosorbent assay (ELISA) method	ELISA results from two different groups of 230 and 50 plasma samples agreed 100 % with APOE genotypes when it came to figuring out who carried APOE 4 and who didn't. This ELISA setup failed to discriminate APOE ε4 homozygotes from heterozygotes, even though plasma samples from homozygous APOE ε4/4 tend to have higher absorbance values than those from APOE ε3/4 and ε2/4 heterozygotes.	[56]
	Polymerase chain reaction-gold magnetic nanoparticles lateral flow assay (PCR-GoldMag LFA)	ApoE genotyping is important because it can help predict the course of heart disease and Alzheimer's. A precise ApoE genotype was determined from all samples. E2, E3, and E4 had 6.98 , 80.48, and 12.54 % allele frequencies, respectively, in the 305 samples studied. Direct DNA sequencing findings were consistent with all genotyping outcomes.	[57]
APP	Sanger sequencing of exon 16 and exon 17	Screening might make it easier to find the real genetic loci linked to the sporadic form of the illness. In the sporadic early-onset Alzheimer's disease [sEOAD) cohort, LOAD was associated with a 6-bp deletion (rs367709245; IVS17 83-88delAAGTAT) and an increase in MAF that was not statistically significant compared to controls. It is impossible to determine if rs367709245 is linked with the illness due to the limited power of the study.	[58]
	Next-generation sequencing	APP c.1810C.T.,p.V604 M is a new mutation located in exon 14. A 3D protein structure model showed that the V604 M swap might modify APP activities owing to methionine's enhanced hydrophobicity in the helix.	[59]
	Genome-wide association study (GWAS)	One of eight 21q21-linked families had a non-synonymous mutation in exon 17 (Val717Leu), while another had a partly penetrating duplication of the 3.5 Mb APP gene. Another family was found to have a 380 kb duplication of the APP gene, which was uncovered by a copy number variation study of the APP region.	[60]
PS1	Whole genome sequencing	A presenilin 1 (PS1) gene mutation (c.356C>T, p.T119I) has been linked to the frontotemporal form of AD using whole-genome sequencing. Late-onset cognitive impairment and early mental symptoms were seen in relatives.	[61]
	Whole-exome sequencing (WES)	Through WES analysis of three generations of a Chinese FAD family, the pathogenicity of the PSEN1 p.Phe177Val variation in FAD was verified. The PSEN1 p.Phe177Val mutation causes a broader range of clinical phenotypes in FAD patients.	[62]
	Next generation sequencing	p.Thr119Ile (c.356C>T), p.Gly209Ala (c.626G>C), and p.Gly417Ala (c.1250G>C) are the three known mutations in PSEN1. PSEN1 p.Tr119 Ile was reported in a patient with EOAD whose condition manifested itself at the age of 64.	[63]
PS2	Whole-exome sequencing (WES)	Changing PSEN2 Thr421 from threonine to methionine may lead to pathogenicity by altering the protein's structure through changes in local protein dynamics. PSEN2 Thr421Met may interact with other neurodegenerative disease-related gene mutations in the proband patient, such as ATP-binding cassette subfamily A member 7; Notch receptor 3; and Leucine-rich repeat kinase 2.	[64]
	Polymerase chain reaction [PCR)	The discovery of a novel mutation in the PSEN2 gene close to the C-terminal end of the protein in a family with early-onset AD supported variable clinical expression due to PSEN2 mutations. At position 430, the PSEN2 gene has a missense mutation, which means that the protein will likely change from threonine to methionine.	[65]

Conclusions

The sixth greatest cause of mortality in Western nations, AD is also the most frequent type of dementia. It is now understood that the extended prodromal phase of late-onset Alzheimer's disease, which frequently starts in midlife, may last for decades before a dementia diagnosis is made. Preclinical AD is the earliest portion of the prodromal phase of AD. At this point, there are no detectable cognitive signs, yet there is a considerable opportunity for early intervention. Evidence that keeps coming in has been very important in figuring out which age groups should be the focus of therapies to lower the risk of AD. In adults over the age of 85 (when Alzheimer's disease dementia is more common, affecting over 30 percent of the population), brain deterioration often begins between the ages of 55 and 65. Comparatively, brain damage in adults aged 65 (at which age around 10 % had acquired dementia owing to AD) also started between the ages of 35 and 45 [14].

A person with AD in the early stages may still be able to take care of themselves and engage in meaningful activities such as driving, working, and socializing. Nevertheless, memory loss, difficulty doing ordinary duties at work or home, forgetting what was just read, losing or misplacing precious goods, and having trouble attempting to plan or arrange schedules or physical spaces are all frequent challenges early in the course of AD. Several years might pass in AD's middle stage. At the middle stage of AD, people may become more sad or shy, forget their address, phone number, or high school or college, need help choosing clothes that fit the season or occasion, and get lost or confused about where they are in space. In the later stages of AD, a person's memory and cognitive abilities keep getting worse, making it hard for them to respond to their surroundings in the right way. They can't follow discussions, talk logically, or say what's going on around them. As it gets harder for them to move their fingers, hands, and feet, it gets harder for them to walk, sit, and swallow. Furthermore, they tend to continue going through personality changes, such as being more prone to outbursts and bouts of laughter and experiencing memory and cognitive decline [66].

Cognitive impairment and neurodegenerative changes that are damaging to neurons define AD, a chronic and progressive neurodegenerative condition. Activated glial cells develop around senile plaques due to Aβ deposition, and these cells produce cytokines, chemokines, and neurotoxins, including reactive oxygen species and nitric oxide, causing the continuing neuroinflammatory process in AD [67]. Approximately 60 % of dementia cases are caused by AD, which is defined by the build up of two proteins: internal neurofibrillary tangles of hyperphosphorylated tau and extracellular Aβ plaques. This is followed by neuronal cell loss, inflammation, and, eventually, death [68].

Older people are the most likely to suffer from AD, as its prevalence increases with age. Two major types of the disease occur: familial and sporadic. Genetic changes in *APP*, *PSEN1*, or *PSEN2* cause an increase in the synthesis of abnormal Aβ fragments and, as a result, an amyloid pathology of increasing plaque. Mendelian inheritance governs the development of familial AD, with a small amount of environmental exposure [69]. Current therapies for AD symptoms include cholinesterase inhibitors, NMDA-receptor antagonists, and combination therapy. AD is also caused by neuroinflammation, oxidative stress, low blood sugar, vascular dysfunction, metal dyshomeostasis, protein misfolding, and abnormal protein clearance [34].

AD is a complex disease that manifests itself with disorders in more than one pathway and at many levels. Genetic predisposition has a major role in AD development. The main microscopic changes in Alzheimer's disease are neurofibrillary tangles accumulating within neurons, amyloid plaques with extracellular deposition, and neuronal loss. Neurofibrillary tangle pathology in AD progresses in parallel with clinical symptoms in the brain. Studies show that APOE allele dosage is associated with increased neurotic plaques in AD. It is still not clear how the abnormal buildup of amyloid affects neurons and nicotinic acetylcholine receptors, or how the disruption of cholinergic pathways leads to cognitive problems in AD. More information about the molecular pathophysiology and connections of AD could lead to new ways to treat the disease and stop it from starting or getting worse [70].

Neuropathological variability in AD may possibly affect future treatment methods. With the change from the amyloid cascade model to a more equipotent view of Alzheimer's disease, the recent focus on anti-amyloid therapies has not been very successful. Even if amyloid pathology is eradicated in an equipotential model of AD, other AD-related pathologies may already be present, continue to grow, and negatively impact cognition. Tau-altering pharmacologic therapies may be useful as tau pathology is more strongly related to clinical and cognitive deterioration than amyloid pathology and may build in sensitive regions sooner than amyloid. Arteriolosclerosis, blood–brain barrier dysfunction, and α-synuclein may combine with aberrant amyloid and tau in older people with sporadic "AD dementia" and need specific treatments [71].

Disease pathogenesis affects blood, cell, tissue, and CSF metabolite concentrations. Metabolic shifts have been connected to a wide range of factors, including genetic

variants, the immunological response, the microbiome, and lifestyle and food. Recent investigations found that plasma phospholipids were connected with cognitive loss in patients with moderate cognitive impairment and AD, and early-stage AD patients had changed sphingomyelin and ceramide levels. CSF Aβ level and monounsaturated sphingomyelins are strongly connected with glucosylceramides, lysophosphatidylcholines, and unsaturated triacylglycerides, whereas ceramides are favorably correlated with CSF total tau and brain atrophy [72].

The relationship between amyloid-β and tau protein buildup and AD-associated genomic damage is crucial. In fact, both of these misfolded proteins linked with Alzheimer's disease are able to produce reactive oxygen species (ROS), with the impact of tau being mediated through mitochondrial malfunction. Tau can also cause breaks in double-stranded DNA, which could make the effect of sSNVs even stronger and possibly cause other mutations. Nonetheless, amyloid β-stimulated activation of microglia, which can directly generate ROS and also indirectly generate ROS through the release of pro-inflammatory cytokines, may be an important component of the oxidative stress caused by AD proteins [73].

We believe that by identifying the genes involved in the molecular pathways associated with Alzheimer's disease, it will be possible to take new steps in the treatment of AD by illuminating the pathophysiology of the disease. Understanding the pathophysiology of AD and other tauopathies will necessitate quantification of physiological and pathological tau. New knowledge about the mechanisms underlying existing diseases will make disease-modifying techniques possible in the future. Further investigations on Aβ-targeted therapy candidates will improve diagnostic accuracy and identify biomarkers that boost the likelihood of therapeutic benefits.

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