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Review

Clinical Epidemiology and APOE Gene Etiology: An Update on Alzheimer's Disease

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ABSTRACT

This review discusses the discovery, epidemiology, and gene etiology of Alzheimer's disease (AD). It also highlights the Alzheimer's gender disparity common comorbid and modifiable risk factors. AD is a progressive neurodegenerative condition that impacts both daily activities and social interactions. With the rise in life expectancy and demographic aging, the global prevalence of AD is expected to increase further, particularly in developing peoples, resulting in a significant burden of disease. Its prevalence in the general population increases dramatically with age; it affects approximately 80% of patients aged ≥ 75 years. AD that occurs before the age of 65, known as early-onset AD (EOAD), is not as extensively studied as late-onset AD (LOAD), even though EOAD often presents with a more aggressive disease progression. AD is a complex and multifactorial disorder influenced by genetic susceptibility and environmental factors over the individual's life. Sex-specific risk factors of dementia for women, including pregnancy, menopause, and preeclampsia, account for the rise of AD among women compared to men. Identifying modifier genes has facilitated the control of APOE genes and their co-expressed genes. Nevertheless, exploring new gene modifiers may enhance a better understanding of intricate AD characteristics and hold potential therapeutic benefits for individuals with AD.

Keywords: Alzheimer's disease; Clinical epidemiology; Gene etiology; APOE, gene modifiers; Functional enrichment analysis

Background

Alzheimer's disease (AD, MIM 104300) is the leading cause of dementia, characterized by a decline in cognitive abilities, functioning, and behavior[1], occurring with approximately 50 million people currently living with dementia worldwide[2]. The aging population is expected to cause this number to triple by 2050[3]. This surge in cases poses a higher risk of disability, increased burden of illness, and rising healthcare costs[3]. The prevalence and incidence of AD significantly rise with age, reaching about 80% of patients aged 75 years or older. The incidence rates increase from 2 per 1,000 individuals aged 65-74 to 37 per 1,000 individuals aged > 85[4]. The majority of AD cases occur after reaching ≥ 65 years and are commonly referred to as late-onset AD (LOAD), whereas cases aged < 65 are infrequent (less than 5% of cases) and are classified as early-onset AD (EOAD)[5].

A precise diagnosis is challenging for individuals experiencing cognitive dysfunction. The decisive pathological characteristics found in the brain tissues of individuals with AD include elevated levels of both amyloid-β (Aβ) forming extracellular senile plaques and hyperphosphorylated tau (p-tau) accumulating intracellularly as neurofibrillary tangles (NFTs)[6]. While AD is typically indicated by Aβ and tau biomarkers, some cognitively normal individuals who exhibit only these

biomarkers do not progress to AD[7], highlighting the challenges in obtaining a pre-symptomatic diagnosis for those individuals.

While there is sufficient evidence on the prevalence of AD in Europe and North America, data is scarce in South and Southeast Asia, Africa, the Middle East, Russia, Eastern Europe, and Latin America[8,9]. Although there are no recognized clinical trials for a cure, AD-modifiable risk factors and prevention, including psychosocial interventions, education, and lifestyles, can help lower the likelihood of AD or postpone its onset. This review discusses the discovery, epidemiology, and gene etiology of AD, particularly APOE. It also highlights AD's gender disparity and specific comorbid and functional enrichment database outcomes.

The Early History of AD

Earlier, in 1901, Alois Alzheimer investigated a female patient admitted at Frankfurt Hospital-Germany, who exhibited various behavioral and psychiatric symptoms, including paranoia, delusions, hallucinations and impaired memory[10]. Later, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-AD & DA) outlined the most common criteria of the disease[11]. These criteria for a probable diagnosis of Alzheimer's include dementia as determined by the mini-mental state examination (MMSE),[12] which allows a brief quantitative measure of cognition status to be determined. It can be used to measure cognitive decline, document cognitive changes over time and with treatment, and as an effective tool in screening for elements of cognitive impairment[12].

Epidemiology

Incidence and Mortality Rates

The global number of individuals who have dementia is estimated to reach 152 million by the middle of the century. This increase is expected to be most significant in low- and middle-income countries[3]. The number of Alzheimer's patients aged 65 and above in The United States may rise significantly from 5.8 million to 13.8 million by 2050 (2020 Alzheimer's disease facts and figures). The prevalence of AD has notably increased in community-dwelling studies conducted in Japan and China over the past few decades[13,14]. Moreover, the age-specific global prevalence in women is 1.17 times higher than in men. The age-standardized mortality rate for women is also greater, indicating that a longer lifespan alone does not account for women's higher prevalence[15].

According to current estimates, there are approximately 6.7 million individuals in the United States who are 65 years and older and are currently living with Alzheimer's dementia[16]. However, if there are no significant advancements in medical research to prevent, slow down, or cure AD, this number could potentially increase to 13.8 million by 2060. In 2019, official death records documented 121,499 deaths caused by AD, making it the sixth-leading cause of death in the United States[16].

Furthermore, numerous risk factors may contribute to the onset of AD and also manifest as symptoms of AD at the same time, suggesting a potential reverse causality. Between 2020 and 2021, COVID-19 emerged as one of the top ten leading causes of death, while AD held the seventh position. Among Americans aged 65 and above, AD continues to be the fifth-leading cause of death. Notably, from 2000 to 2019, fatalities resulting from stroke, heart disease, and HIV declined, whereas reported deaths attributed to Alzheimer's disease witnessed a significant increase of over 145%[16].

Gender Disparities

Gender and age disparities are seen in cognitive disturbances in various neurological and psychiatric disorders. Multiple environmental, behavioral, and lifestyle factors have been linked to AD, and the associations between several of these risk factors and dementia differ based on sex and gender[17]. The number of individuals affected by AD is increasingly rising at a greater rate in women compared to men in the future. This trend is attributed to the increased lifespan of women and biological factors[4]. The overall risk of developing AD for individuals aged 65 is 21.2% for females and 11.6% for males[3,18]. The expected survival duration for AD varies from four to eight years across different studies. It is influenced by various factors such as age at diagnosis, gender, behavioral characteristics, involvement of the motor system, and co-existing medical conditions[19]. Sex-specific risk factors of dementia for women, including pregnancy and menopause, have demonstrated that a history of preeclampsia increases the risk of mild cognitive impairment, vascular dementia, and AD[20-23]. Moreover, early menopause before the age of 45 has been associated with an increased risk of mild cognitive impairment and dementia.

It is still uncertain if there is an association between low testosterone levels and the risk of dementia in males[24]. However, sex steroids can have a positive impact on brain function, and lower levels of these hormones may be linked to poorer cognitive function in older men[25,26]. On the other hand, previous studies have presented conflicting findings regarding the relationship between testosterone levels and the risk of AD in older men[27-29]. A meta-analysis study involving 5,251 older men and 240 cases of AD revealed a significant association between low testosterone levels and an increased risk of the disease (random relative risk = 1.48, P = 0.006)[30]. Nevertheless, androgen deprivation therapy, a widely used treatment for prostate cancer, has been linked to an increased risk of cognitive impairment and dementia[31].

Clinical Characteristics of AD

Age is commonly recognized as a primary risk factor for AD and is utilized in two categories[32,33]. The two primary subcategories of the disease encompass early-onset AD (EOAD) and late-onset AD (LOAD). These classifications are assigned when individuals typically exhibit symptoms, usually around 65 years old[33]. However, it may occur earlier in cases where genetic mutations in familial Alzheimer's disease (FAD) genes are involved. AD symptoms typically accompany numerous cognitive impairments in various areas, including visuospatial, language, and executive function[34].

Late-Onset AD

Typically, the clinical manifestation of AD is primarily marked by a significant decline in anterograde episodic memory. This symptom is commonly seen alongside various cognitive deficits like visuospatial abilities, language skills, and executive function[34]. The presence of these specific AD features collectively results in an overall cognitive deterioration, ultimately culminating in complete dependence and mortality[35]. In the late stage of AD, magnetic resonance imaging may observe ventricular enlargement and shrinkage of the brain. Various alterations observed in the AD brain include neuronal loss in specific areas, intracellular neurofibrillary tangles within the neurons of the cerebral cortex and hippocampus, and neuritic plaques composed of amyloids that dystrophic neurites, reactive astrocytes, and microglia could encircle[36-38].

Early-Onset AD

Although the typical manifestation of memory-predominant phenotypes overlaps between LOAD and EOAD cases, some EOAD cases exhibit atypical patterns where episodic memory remains intact while experiencing specific cortical symptoms associated with language, visuospatial abilities, or executive function[35]. As the disease progresses, a specific set of non-memory symptoms is observed in approximately 25% of cases with EOAD. These symptoms include apraxia, visual dysfunction, fluent or non-fluent aphasia, executive dysfunction, or dyscalculia[39-42]. Significant disparities in the onset age exist both within and across families, partly attributed to genetic, environmental, or random factors[41]. While some autosomal dominant cases develop first symptoms as early as their late 20s, others develop the disease in their early 60s (prevalence increases with age)[42]. Finally[43], reported that, in families with PSEN1, PSEN2, or APP-caused AD mutations, the characteristics of neuroticism and conscientiousness were linked to the time until symptoms appeared, indicators of tau pathology in the cerebrospinal fluid (CSF), and the progression of cognitive decline over time[39].

Modifiable Risk and Protective Factors

Multiple longitudinal investigations have pinpointed a range of risk and protective factors associated with AD, some of which may be addressed to lower the likelihood of AD or postpone its onset[44-48]. AD is believed to begin decades before any noticeable clinical symptoms manifest. As a result, addressing multiple risk factors in non-demented elderly individuals, even the middle-aged population, could potentially help in either preventing or postponing the onset of AD[47]. Efficient preventive efforts can potentially hinder the progression of AD. Additional policies to promote education and raise awareness about social or cognitive activities should be proposed to the general public. In addition, maintaining healthy lifestyles and protecting against air pollutants in the environment is crucial for preventing AD[47] **(Figure 1)**.

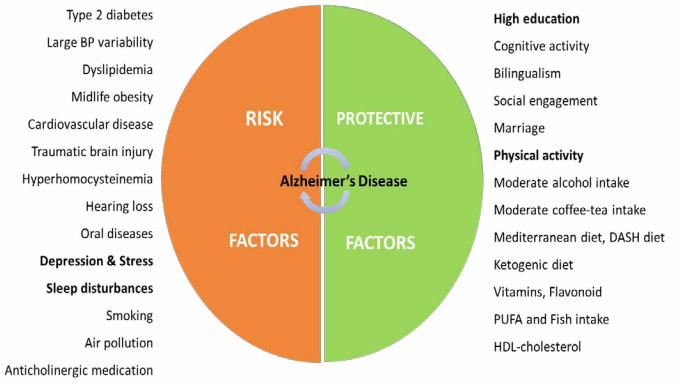

Figure 1: Modifiable risk and protective factors. Some factors appeared to be risk factors and symptoms of AD, possibly due to the reverse causality, as shown in bold.

Abbreviation: BP = blood pressure, DASH = Dietary Approach to Stop Hypertension, MIND = Mediterranean-DASH diet Intervention for Neurodegeneration Delay, PUFA = polyunsaturated fatty acid, HDL-cholesterol = high-density lipoprotein cholestero[47].

Genetic Etiology

The genes implicated in early-onset forms of AD, which occur below 65 years of age, are the APP gene located on chromosome 21q21 (MIM 104760); PSEN1 located on chromosome 14q24.3 (MIM 104311) and PSEN2 on chromosome 1q31-q42 (MIM 600759). Missense mutations within the PSEN1 gene account for 18-50% of AD's early-onset autosomal dominant forms[49]. Mutations within the PSEN1 gene lead to an aggressive form of the disease, with an onset age between 30 and 50 years, which is not influenced by the APOE genotype. However, a polymorphism found within intron 8 of the PSEN1 gene was associated with developing the late-onset form of AD[50,51]. PSEN1 and PSEN2 account for less than 5% of AD cases[51-54].

Regarding the APP (MIM 104760), Glenner and Wong[55] previously isolated a protein from the twisted beta-pleated sheet fibrils found in cerebrovascular amyloidoses and amyloid plaques associated with AD (MIM 104300)[56]. determined in a comprehensive study of familial and sporadic EOAD that mutations in the APP gene only explain a small fraction of FAD cases. The average age of disease onset in individuals with APP gene mutations was 51.2 years. Taking into account previous research[57], approximated that 16% of early-onset AD cases are linked to mutations in the APP gene.

Genetic variations in promoter sequences that modify gene expression influence susceptibility to complex diseases. The expression levels of APP are primarily controlled by its core promoter and the regulatory region upstream of the 5-prime end, which is linked to amyloid beta levels in AD brains. In a study involving 427 French patients with LOAD[58], identified a significant relationship between a -3102G/C SNP (rs463946) located in the 5-prime region of the APP gene and AD. This association was confirmed in a separate group of 502 AD cases. The C allele was protective (OR, 0.42; P = 5E-4)[59]. Reported on recombining the APP gene in both normal and AD neurons, manifesting as numerous variant genomic cDNAs. Neurons from individuals with sporadic AD exhibited a higher diversity of genomic cDNAs, including 11 mutations associated with FAD that were not present in healthy neurons.

APOE Associated with AD

Understanding the genetic variants of APOE ε4 carriers has highlighted the APOE pathophysiology and resistance to AD, offering potential therapeutic benefits. Thus, multiple genome-wide association studies (GWAS) and meta-analyses[60] demonstrated that the APOE gene (ε4 allele) remains the most common genetic risk factor associated with sporadic AD when compared to the more prevalent ε3 allele. In addition[61], found that APOE ε2 homozygosity was associated with much lower odds of AD than APOE ε3 homozygosity. Thus, the difference between APOE ε2 homozygosity and APOE ε4 homozygosity was even more pronounced (0.004 [0.001- 0.014]), and APOE ε2 was linked to milder AD neuropathological changes (i.e., fewer Aβ plaques and neurofibrillary tangles)[62].

A 70-year-old Colombian woman with a fully penetrant autosomal dominant E280A mutation in the PSEN1 gene, associated with FAD and abundant fibrillary Aβ deposits, remained cognitively healthy longer than expected. However, her resilience to AD was due to a rare R136S gene mutation in APOE ε3 Christchurch[63]. The resistance against AD was explained as the APOE3 R136S mutation works mechanistically by inhibiting Aβ oligomerization, disrupting APOE binding to LDL receptors, and interfering with APOE affinity for heparan sulfate proteoglycans. These proteoglycans are involved in the

uptake of toxic tau by neurons, which may explain the lower-than-average radioligand uptake observed in her tau PET scan[64].

Modifier Genes

Recent discoveries in modifier genes in various brain cell types have opened up new avenues for treating and halting the advancement of numerous neurological[65-67] and neurodegenerative conditions, including AD[62,68]. These modifier genes can alter the expression of other target genes and influence the penetrance, severity, or other clinically important features of diseases caused by rare mutations in target genes. Notably, a significant portion of FAD cases are associated with missense mutations in APP, presenilin 1 (PS1), and presenilin 2 (PS2), prompting extensive research to identify proteins that interact with PS1 and PS2 due to their crucial roles in FAD[69].

A meta-analysis study has revealed that KLOTHO-VS heterozygosity, a polymorphism previously associated with longevity, might reduce the increased AD risk associated with the APOE ε4 allele. A mainland Chinese cohort underwent genome sequencing, revealing nine potential causal variants in two genes at the APOE, PVRL2, and APOC1 loci[70]. These variants were found to elevate the susceptibility to AD regardless of the presence of the APOE ε4 allele. The whole genome sequencing data stratified by APOE genotype identified three genes significantly associated with AD in APOE4 carriers only: OR8G5 (P= 4.67E10−7), SLC24A3 (P= 2.67E−12), and IGHV3-7 (P= 9.75E-16)[71]. Recently, SLC22A17 has been recognized as a promising drug target for developing interventions to boost neurogenesis in AD[72]. Conversely[73], explored the genetic foundation of resilience to AD in APOE ε4 homozygotes. They showed that CASP7 (which encodes caspase 7) rs10553596 and SERPINA3 (which encodes α1-antichymotrypsin) rs4934-A/A polymorphisms may lower the risk of AD[73].

Protein-Protein Interactions In Apoe Co-Expressed Genes

We examined the network interactions of the amyloid-beta precursor protein (APP) and co-expressed genes using the STRING software, as shown in **(Figure 2).** Interestingly, the APP network and 14 co-expressed proteins, including APOE, APOC1, APH1A/B, PSEN1/2, PVRL2, BACE2, and NCSTN, exhibited a significantly higher number of interactions among themselves (P< 1.0E−16) compared to what would be expected for random proteins of similar size and distribution from the genome. This enrichment suggests a partial biological connection between these proteins. Notably, the previous SLC24A3, KRTCAP2, SLC22A17, and OR8G5 genes[71] assigned to Alzheimer's individuals have not interacted or co-expressed with the APP network **(Figure 2)**.

Functional Enrichment Analysis

Table 1 highlights the biological enrichment of APP and related proteins, including APOE, APOC1, APH1A/B, PSEN1/2, PVRL2, BACE2, and NCSTN) in biological and molecular functions, including amyloid-beta, Notch receptor processes & tau protein binding, and cellular components, including gamma-secretase complex (GO:0070765), triglyceride-rich, low, and chylomicron lipoproteins. Furthermore, KEGG pathway analysis revealed the Alzheimer's disease, Notch signaling (hsa05010), and 'Pfam' revealed the apolipoprotein C-II, A1/A4/E domains (PF05355) **(Table 1)**.

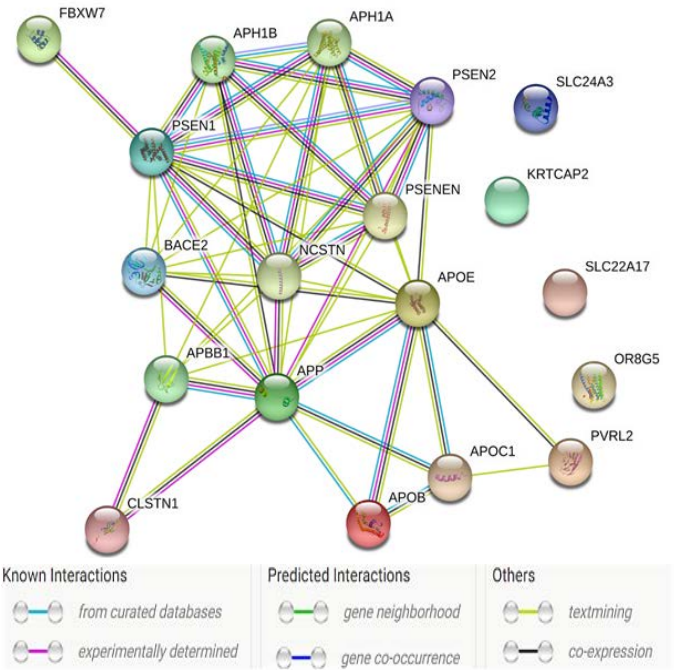

Figure 2: Protein-protein interactions predicted by STRING (https://string-db.org/). Strong interactions were predicted between APP and 14 co-expressed proteins. Colored nodes (n= 19) represent proteins and the first shell of interactors (average node degree= 5.37). Edges represent specific and meaningful protein-protein associations (n= 51) (i.e., proteins jointly contribute to a shared function).

Table 1: Functional enrichment in APOE protein-coding gene loci network.

GO-term	Description	count in network[a]	FDR[b]
Biological functions (GO):			
GO:0035333	Notch receptor processing, ligand-dependent	7-Jun	9.35E-13
GO:0033619	membrane protein proteolysis	Jul-36	3.83E-12
GO:0042982	amyloid precursor protein metabolic process	16-Jun	1.01E-11
GO:0050435	amyloid-beta metabolic process	16-Jun	1.01E-11
GO:0006509	membrane protein ectodomain proteolysis	20-Jun	1.78E-11
GO:0042987	amyloid precursor protein catabolic process	9-May	1.90E-10
GO:0007219	Notch signaling pathway	7/116	2.69E-09
GO:0016485	protein processing	7/142	9.43E-09
GO:0034205	amyloid-beta formation	5-Apr	1.14E-08
GO:1905908	positive regulation of amyloid fibril formation	4-Mar	3.28E-06
GO:0034447	very-low-density lipoprotein particle clearance	6-Mar	7.31E-06
GO:0034382	chylomicron remnant clearance	8-Mar	1.34E-05
GO:0043085	positive regulation of catalytic activity	10/1381	1.50E-05
GO:0046890	regulation of lipid biosynthetic process	5/174	5.25E-05
GO:1901214	regulation of neuron death	4/288	0.0027
GO:0007613	memory	3/109	0.0028

GO:1904646	cellular response to amyloid-beta	26-Feb	0.0044
Molecular Function (GO):			
GO:0001540	amyloid-beta binding	Apr-57	5.10E-05
GO:0004175	endopeptidase activity	6/399	0.00013
GO:0004190	aspartic-type endopeptidase activity	24-Mar	0.00013
GO:0042277	peptide-binding	5/270	0.00013
GO:0050750	low-density lipoprotein particle receptor binding	22-Mar	0.00013
GO:0042500	aspartic endopeptidase activity, intramembrane cleaving	6-Feb	0.00036
GO:0060228	phosphatidylcholine-sterol O-acyltransferase activator activity	6-Feb	0.00036
GO:0048156	tau protein binding	18-Feb	0.0019
Cellular component (GO):			
GO:0070765	gamma-secretase complex	6-May	4.62E-11
GO:0034385	triglyceride-rich plasma lipoprotein particle	21-Apr	5.45E-07
GO:0034363	intermediate-density lipoprotein particle	6-Mar	3.35E-06
GO:0035253	ciliary rootlet	10-Mar	5.69E-06
GO:0042627	chylomicron	13-Mar	8.09E-06
GO:0034361	very-low-density lipoprotein particle	20-Mar	2.00E-05
GO:0034364	high-density lipoprotein particle	28-Mar	4.72E-05
GO:0005794	Golgi apparatus	9/1474	4.75E-05
GO:0005790	smooth endoplasmic reticulum	31-Mar	5.23E-05
GO:0043198	dendritic shaft	Mar-37	8.15E-05
GO:1990761	growth cone lamellipodium	3-Feb	9.21E-05
KEGG pathway (HSA):			
hsa05010	Alzheimer's disease	10/168	3.59E-15
hsa04330	Notch signaling pathway	Jun-48	6.09E-11
hsa04979	Cholesterol metabolism	Mar-48	7.30E-05
hsa04722	Neurotrophin signaling pathway	2/116	0.0201
Reactome pathway (HSA):			
hsa-174824	Plasma lipoprotein assembly, remodeling, clearance	26-Feb	0.00043
hsa-109582	Hemostasis	3/591	0.0076
hsa-1430728	Metabolism	4/1420	0.0081
Protein domains & families (Pfam):			
PF05355	Apolipoprotein C-II	2-Feb	4.65E-05
PF01442	Apolipoprotein A1/A4/E domain	4-Feb	5.81E-05

FDR false discovery rate (highly significant), GO gene ontology, KEGG Kyoto Encyclopedia of Genes and Genomes.

[a]Proteins in the examined network/total number of proteins.

[b]Log10 (observed/expected), describing the extent of the enrichment effect.

Conclusion And Future Directions

This review discusses the discovery, epidemiology, and gene etiology of Alzheimer's disease (AD). It also highlights the Alzheimer's gender disparity common comorbid and modifiable risk factors. Globally, AD prevalence in the general population increases dramatically with age; it affects approximately 80% of patients aged ≥ 75 years. Recent discoveries in modifier genes in various brain cell types have opened up new avenues for treating and halting the advancement of numerous neurological and neurodegenerative conditions, such as AD. Importantly, the review's content can guide upcoming health research on AD and provide clinicians with evidence-based data regarding APOE and co-expressed genes.

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