sciendo Acta Marisiensis - Seria Medica 2024;70(4):205-215 DOI: 10.2478/amma-2024-0030

REVIEW

The genetic landscape of early and late-onset Alzheimer's disease: A review

Paula Denisa Saragea*

Department of Biology, "Alexandru Ioan Cuza" University of Iasi, Romania

Alzheimer's disease(AD) is a multifactorial neurodegenerative disorder characterized by the progressive loss of neurons and synaptic dysfunction, primarily affecting the cortex and hippocampus. The etiology of AD is complex, involving the continuous and intricate interaction between genetic and non-genetic environmental factors. Genetic predisposition plays a significant role, with approximately 60-80% of AD risk attributed to hereditary factors. Familial early-onset AD(EOAD), with autosomal-dominant mutations in APP, PSEN1, and PSEN2, represents about 1-5% of cases and typically manifests before age 65. Rare autosomal-recessive mutations, like A673V(APP gene), are also implicated. Late-onset AD(LOAD), more common, is influenced by a combination of genetic and environmental factors, with the APOE ε4 allele being a major risk factor. Protective factors, such as the APOE ε2 allele and rare mutations like Ala673Thr, can reduce AD risk. The interplay between genetic variants, environmental influences, and pathological processes underpins the disease's progression. This study highlights the importance of understanding the genetic and non-genetic determinants of AD to advance personalized treatment and early detection strategies. Future research and personalized medicine approaches are essential for mitigating AD risks and improving management outcomes.

Keywords: Alzheimer's disease, multifactorial, genetics, hereditary, genetic predisposition

Received 30 August 2024 / Accepted 24 September 2024

Introduction

General Overview – Multifactorial Diseases And The Interaction Between Environment And Heredity

Within the broad spectrum of chronic neurological disorders, Alzheimer's disease (AD) is defined by neurodegenerative processes that involve synaptic dysfunction due to the depletion of acetylcholine and other neurotransmitters, as well as irreversible degradation and continuous loss of neurons in specific regions of the cortex and hippocampus. These affected areas, along with distinctive molecular and cellular markers, delineate and shape the clinical picture with a high degree of accuracy. Establishing the genetic etiology of this disorder dictates the need to identify the type of transmission, as AD is inherently heterogeneous and multifactorial. The determination of the genetic etiology of this condition underscores the importance of identifying the inheritance patterns, as AD represents a heterogeneous, multifactorial disorder.

AD is a multifactorial, neurodegenerative, and polygenic condition that develops under the influence of both genetic and non-genetic determinants, including environmental, behavioral, demographic, pathological and physiological risk factors. These multifactorial diseases emerge in human organisms—each a unique biological entity—due to interactions between genetic inheritance and environmental influences, or, in rare instances, due to one of these factors alone (Figure 1). In these exceptional and uncommon instances, genes may follow a monogenic pattern of inheritance, being passed down through either autosomal-recessive inheritance(A673V-APP gene) or autosomal-dominant inheritance (PSEN1 on chromosome 14, PSEN2 on chromosome 1, and APP on chromosome 21) [1–8].

Hereditary factors can determine a person's genetic predisposition to be affected by a certain disease throughout their life. However, the transition from a vulnerable state to the actual onset of the disease occurs through the continuous interplay of the two major classes of factors (only when the intervention of environmental factors exceeds a threshold that triggers the disease). This explains why some individuals with a genetic predisposition remain healthy if they are not exposed to triggering environmental factors, or why those who encounter harmful factors may remain unaffected due to their genetic resilience. Thus, disease emerges as the result of a complex, bilateral interaction between genetic and environmental factors [9–12].

Studies focused on the heritability of AD have found that environmental factors contribute only 20-40% to shaping a person's risk, while genetic determinants contribute between 60-70% and 80% to the onset of this neurodegenerative condition [13,14].

Motivation and Objectives

The exploration of neurodegenerative processes in this study simultaneously encompasses two intertwined dimensions: an objective one, driven by the innate curiosity, pure desire to expand the boundaries of knowledge and to deepen the understanding of these complex, intricate conditions, and a subjective one, triggered by the forced confrontation and acceptance of the poignant, inescapable, and harsh reality of being a mere witness/spectator, without the power to alter or influence the narrative thread of the unfolding drama, where a loved one gradually loses

* Correspondence to: Paula Denisa Saragea
E-mail: paula_denisa_2000@yahoo.com

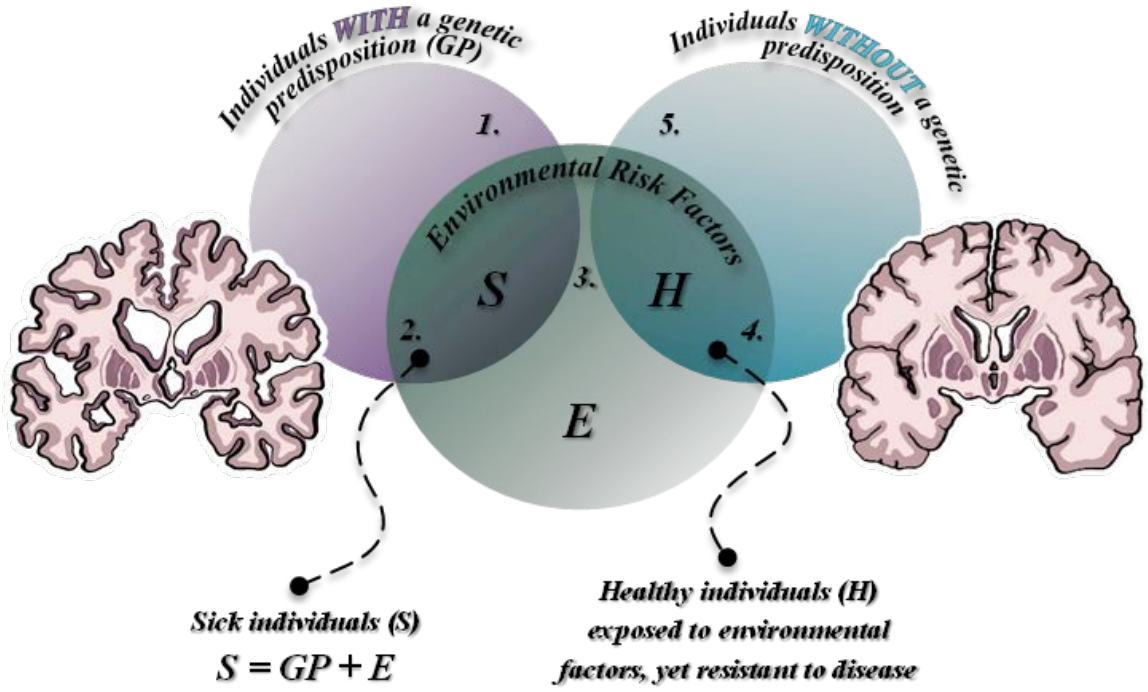

Fig. 1. Interaction between Genetic and Environmental Factors in the Determinism of Multifactorial Diseases; S=Sick individual; H=Healthy individual; E=Environmental risk factors; GP=Genetic predisposition; 1=Individuals with genetic predisposition to Alzheimer's disease (GP); 2=Individuals diagnosed with Alzheimer's disease, affected by the interplay of environmental and hereditary factors; 3=Environmental factors exposure; 4=Healthy individuals exposed to environmental risk factors but resistant to disease; 5=Individuals without genetic predisposition;

fragments of what once defined them, facing progressive cognitive, functional, and behavioral decline. This journey, steeped in a profound sense of loss, reveals the tragic beauty of a mind gradually surrendering its essence, as personality defining fragments slowly fade away, leaving behind echoes of what once was.

Under the shadow of these relentless and unforgiving neurodegenerative diseases, the human being becomes powerless, incapable of shaping their own future, destiny, or existence once these processes, whether early or late, begin to unfold. Transformed without consent into a puppet of affliction, the patient loses their sense of self, becoming unable to encode or retain information, entirely bereft of independence and consciousness. This dramatic play unfolds in multiple acts, encompassing scenes of various durations that reflect the merciless reality of different stages of the disease, each progressing at its own speed, while the entr'actes within the drama symbolize the stagnant phases of the illness, the plateaus. On the stage of life, the patient in advanced, final stages, recognizable only in material form, is overwhelmed by anxiety, becomes fearful, engulfed by dread, emotionally disturbed, and stripped of a sense of belonging and familiarity. AD thus takes on colossal dimensions, becoming, in a figurative sense, a ruthless and grotesque puppet master devoid of mercy and scruples, suppressing the essence of the central character (the patient diagnosed with AD) and redefining the nature of their existence.

The study aimed to identify genetic predispositions that significantly affect individual health and, in conjunction with non-genetic, modifiable risk factors (Figure 2) contribute to the onset of neurodegenerative processes associated with AD.

Materials and Methods

The information compiled in this study was gathered from university library collections, search engines, and online databases, including Google Scholar, ScienceDirect, and PubMed(MEDLINE). Selection criteria were based on the type of analyzed material (such as books, review articles, meta-analyses, documents, systematic reviews, and original studies) and the publication date. The search was conducted using specific phrases or keywords like „AD", „genetic factors", "genetic counseling", "genetics", "genetic testing" or „risk factors" with filters applied accordingly.

Results and Discussions

Genetic Factors

AD is internationally regarded as a dichotomous condition, encompassing two major clinically defined forms: familial AD, characterized by mendelian inheritance and early onset(<60 years)(EOAD), and late-onset AD(LOAD), which may or may not involve an inherited predisposition and lacks a consistent transmission pattern(≥65 years). While the majority of AD cases have a genetic origin (~80%), ‚sporadic' forms result from the interaction between genetic factors and environmental influences [4].

Genetic factors with causative or protective roles have been studied extensively, starting with twin studies that

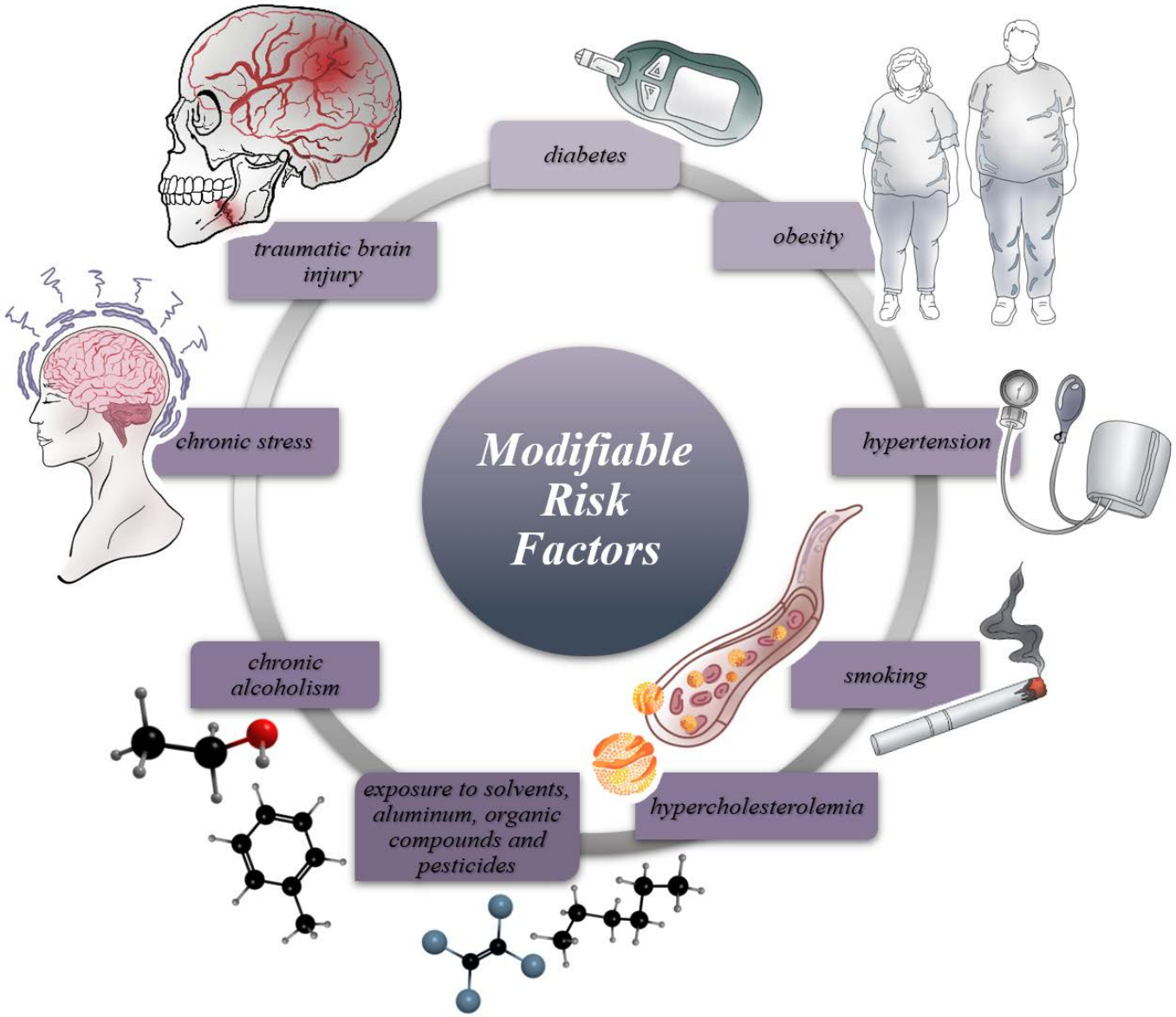

Fig. 2. Non-genetic, Modifiable Risk Factors—demographic, physiological, pathological, behavioral, and environmental—that significantly impact the health of people

indicate the risk of developing AD is determined by hereditary factors to an extent of 60-80%. Although AD is classified as a multifactorial condition, with its decline, rate of deterioration, and onset influenced by both genetic and environmental factors, there are forms of AD with autosomal-dominant or recessive determinism, mendelian inheritance, or polygenic, additive determinism [4,13,15].

Chromosomal mutations involved in the determinism of AD are rare, exhibit mendelian, autosomal-dominant inheritance, and predominantly occur on chromosomes 1, 14, and 21, leading to the development of early-onset forms before the age of 65.

In the particular case of individuals with Down syndrome, also known as trisomy 21 (21q), there will be an overproduction of β-amyloid, leading to the formation of senile plaques as early as the first decade of life. Consequently, individuals diagnosed with Down syndrome, who have an additional copy of the APP gene, will typically develop AD after the age of 40 (and no later than their fifth decade of life) [3,5,16–20].

Being the most well-known form of familial aneuploidy, trisomy 21 (HSA21) is characterized by intellectual impairment, with the additional genetic material leading to a 40% reduction in brain volume in adults and a 90% decrease in neuronal density in the entorhinal cortex. The presence of three copies of the APP gene on HSA21 results in the overexpression of APP, leading to the overproduction of Aβ peptides and the accumulation of insoluble senile plaques in extracellular spaces [21].

Nevertheless, AD is predominantly a multifactorial condition with polygenic determinism. To date, 45 loci have been identified, with risk genes exhibiting additive effects. The identification of the presence or absence of risk genes aids in calculating the polygenic risk of recurrence with an accuracy ranging from 75% to 85%. Both the APOE ε4 allele and the numerous identified loci contribute to

the development of AD symptoms, along with multiple mechanisms involving cholesterol and amyloid metabolism, modulation of immune responses, endocytosis, lipid dysfunction, and vascular factors [16–18,22].

The polymorphism with the highest genetic susceptibility identified is apolipoprotein E4, which is simultaneously involved in increasing the risk of cardiovascular diseases and in decreasing the age of onset of AD, as well as accelerating the rate of decline. However, risk alleles have been identified in the majority of patients with LOAD, affecting both heterozygotes and homozygotes for ε4 [16–19,22–24].

Protective genes

The increased interest of researchers in identifying genetic factors responsible for the onset of AD has led to the discovery of some protective factors.

In the case of the gene located on chromosome 21 with autosomal dominant inheritance, a rare ‚Icelandic' protective mutation, Ala673Thr, has been identified. This mutation delays cognitive decline, helps maintain normal cognitive reserves, and reduces Aβ levels by 40%. Next-generation sequencing (NGS) has revealed that this rare variant is significantly more common in individuals without AD—approximately five times more frequent—than in those with the condition [8,13,15,19,22].

Case studies have also highlighted other protective mutations: the ‚Christchurch' mutation, found in an APOE ε3 allele, which confers genetic resilience in patients with a PSEN1 mutation, allowing them to surpass the life expectancy predicted based on the age at which their affected relatives passed away, as well as variations in Klotho, the longevity gene.

Similarly, the protective potential of the APOE ε2 allele has been discovered, with cohort studies revealing that individuals who are homozygous (APOE ε2/ε2) or heterozygous (APOE ε2/ε3, APOE ε2/ε4) for this allele have a twofold lower risk of developing AD.

The PLCG2 gene can undergo a structural modification, specifically Pro522Arg, which halves the risk of carriers developing a form of dementia(AD) and doubles or even triples the likelihood of reaching the tenth decade of life with intact cognitive functions [8,16–19,22,24–27].

Causative Genes

NGS techniques have led to the identification of a broad spectrum of rare variants that contribute to protein degradation processes, with the altered forms leading to the gradual deterioration of brain health [22].

The causative genes identified through genome-wide association studies have multiple implications, acting within the following biological pathways: lipid transport, immune system responses, endocytosis, inflammatory responses, TAU protein metabolism, cytoskeletal functions, processing of the amyloid precursor protein (APP), axonal transport and signaling, synaptic functions in the hippocampus, cell migration, the functioning of myeloid cells and microglia, astrocytes, mitochondrial function and integrity, gene expression regulation, and post-translational modifications of proteins.

The causative genes identified through genome-wide association studies have diverse implications, influencing various biological pathways, including lipid transport, immune system responses, endocytosis, inflammatory processes, TAU protein metabolism, cytoskeletal functions, amyloid precursor protein(APP) processing, axonal transport and signaling, synaptic functions in the hippocampus, cell migration, the activity of myeloid cells and microglia, astrocyte function, mitochondrial integrity and function, gene expression regulation, and post-translational protein modifications [28,29].

Causative genes can be classified according to the pathogenic pathways they influence. According to the study published by Hinz and Geschwind in 2016, there are four distinct categories:

- Causative genes that affect lipid metabolism(cholesterol metabolism) [11,12,14]
  - APOE,DSG2, ABCA7,SORT1,CLU,PLD3
- Causative genes that influence synaptic function, affecting their functionality [11,12,14]
  - PICALM,AKAP9,BIN1,EPHA1,MEF2C,PTK2B,CD2AP
- Causative genes involved in the neuroimmune system(neuroinflammation) [11,12,14]
  - CLU,TREM2,HLAcomplex(HLA-DRB1,HLA-DRB5),CR1,MEF2C,ABCA7,CD33,INPP5D,EPHA1,EPHA2
- Causative genes that influence endocytosis and synaptic transmission [11,12,14]
  - BIN1,CD33,SORL1,PICALM,EPHA1,CD2AP,SORT1

In the context of AD, many genes with fundamental roles in its determinism have been identified over time, especially through genome-wide association studies. These genes can be categorized based on the type of neurodegenerative disorder they induce:

- Major genes associated with EOAD
- Genes associated with sporadic EOAD
- Genes associated with LOAD [4,30–32]

1. Major genes associated with EOAD

- Mutations in the ***PSEN1*** gene, located on chromosome 14, lead to the overproduction of amyloid precursors by affecting the Notch signaling pathway. This occurs due to the activation or enhancement of the enzyme known as γ-secretase [4,16–19,22,24–26].
- Researchers have identified a mutation, ***Gly206Ala***, in the ***PSEN1*** gene specific to individuals of Puerto Rican descent diagnosed with EOAD [4,16–19,22,24–26].
- Mutations in the ***PSEN2*** gene, located on chromosome 1 [4,16–19,22,24–26].
- Mutations in the ***APP*** gene, located on chromosome 21,

include the "Swedish" mutation at the β-secretase cleavage site and the "Arctic" mutation, which promotes the formation of protofibrils and insoluble fibrils by altering the assembly of β-amyloid [4,16–19,22,24–26].

2. Genes associated with sporadic EOAD

The analysis of scientific papers published over time, along with research conducted on extensive cohorts of patients from various continents, has led to the identification of additional mutations that cause familial EOAD, including rare, sporadic forms, in specific geographic regions:

– The ***MAPT*** gene, located on the long arm of chromosome 17 (17q), undergoes a missense point mutation, R406W, which has been detected in a Belgian family [4,30–32].
– A mutation at position 36 on the long arm of chromosome 7 (7q36), near the ***PAX*** transcription activation domain (PAX1P1), has been identified in a Dutch family [4,31].
– A missense point mutation, D90N, in the ***PEN2*** gene located on chromosome 19, has been identified. This gene is involved in encoding the pen-2 component of γ-secretase [4,33].

3. Genes associated with LOAD

In the case of the ***APOE4*** gene, studies have demonstrated that the ε4 allele has the capacity to reduce the clearance of Aβ42 peptides and β-amyloid proteins, leading to their accumulation and subsequent neurotoxic effects on the central nervous system (CNS) [3,8,16–19,22–26,28,34].

– The ***ADAM10*** gene encodes a member of the ADAM family and a major α-secretase, both of which are involved in the early phases of amyloid precursor protein (APP) cleavage, initiating neurodegenerative processes. ADAM10 is crucial for the cleavage of normal prion proteins and interacts with a wide range of proteins, including E-cadherins and TNF-α. The two known mutations, R181G and Q170H, result in the inability to complete the cleavage operation of ADAM10 by α-secretase, including the amyloid precursor protein(APP), both in vivo and in vitro [3,8,16–19,22–26,28,34].
– Another genetic factor implicated in the etiology of LOAD is the ***ABCA7*** gene, located on 19p13.3. This gene encodes a protein specific to multicellular eukaryotes from the major ABC subfamily. The synthesized protein is involved in processes such as phagocytosis and lipid homeostasis in immune system cells, although its functions are not fully understood. However, it is known to be a tissue transporter specific to myelo-lymphatic regions. According to scientific literature, the ABCA7 gene is associated with AD and is detected at a higher frequency among African Americans compared to Caucasian Americans [3,8,16–19,22–26,28,34].
– The ***BACE1*** gene, responsible for encoding a transmembrane protease from the A1 peptidase family, acts catalytically on the amyloid precursor protein. This process releases soluble β-APP peptides into the extracellular space and subsequently the C-terminal fragment within the cell [3,8,16–19,22–26,28,34].
– One of the most relevant risk factors for LOAD, according to the specialized literature, is the ***BIN1*** gene. This gene encodes multiple isoforms of a nucleoplasmic adaptor protein with different tissue distributions, and in the central nervous system, it plays a role in vesicle-mediated synaptic endocytosis. BIN1 is involved in processes such as the activation of pro-inflammatory mechanisms, the production and release of cytokines, and the activation of genes associated with neurodegeneration [3,8,16–19,22–26,28,34].
– Another gene implicated in the etiology of LOAD is ***C9ORF72***. The protein encoded by this gene has multiple roles, including autophagy, coordination of endosomes, axonal growth and extension, regulation of actin activity in motor neurons through the inhibition of GTP binding to ARF6, immune development, and inflammation reduction in the hematopoietic system [3,8,16–19,22–26,28,34].
– The ***CD33*** gene encodes amino acid sequences that form proteins involved in the differentiation pathways of hematopoietic stem cells and the innate immune system. These proteins, through their SH2 domain, bind to a cytoplasmic phosphatase, which dephosphorylates signaling molecules, thereby blocking signal transduction and inhibiting tyrosine phosphorylation—a process critical to the immune responses of host organisms. In the specific context of AD, CD33 plays a role in controlling microglial activation, a process that is also influenced by the expression of TREM2 [3,8,16–19,22–26,28,34].
– The ***CLU*** gene, located on chromosome 8(8p21-p12), encodes the eponymous protein clusterin (APOJ), which is responsible for inhibiting the formation of amyloid fibrils (including APP, B2M, APOC2, SNCA, CSN3, LYZ). Alterations in this gene can lead to the enhancement of these processes, which are characteristic of neurodegenerative phenomena. Both the normal and pathological variants of this protein are involved in coordinating cell death, neuronal destruction processes, and the progression of tumor cells and clones [3,8,16–19,22–26,28,34].
– Studies suggest that a glycosylated peptide plays a role in mitigating processes induced by TAU and β-amyloid proteins by regulating cellular growth, tissue remodeling, and inflammatory responses. Mutations in the gene encoding progranulin (a precursor protein of 88kDa), known as ***GRN***, lead to the loss of these protective processes, thereby increasing the risk of AD onset. This results in neuroinflammation, decreased neuronal survival, and accelerated cognitive decline. Research indicates that progranulin levels are notably low in diagnosed patients. Additionally, the association of progranulin deficiency with the overregulation of cyclin-dependent kinases contributes to the development of hyperphosphorylation

processes [3,8,16–19,22–26,28,34].
– Mutations in the ***MAPT*** gene are associated with various forms of neurodegenerative diseases, including AD. In its unaffected form, the MAPT gene, whose exons are responsible for encoding microtubule-associated TAU proteins, promotes the stabilization and assembly of microtubules and also contributes to the maintenance of neuronal polarity [3,8,16–19,22–26,28,34].
– In pathological cases, particularly in the context of the onset of AD, the ***TARDBP*** gene plays a crucial role. Cognitive decline is also induced by the emergence of hyperphosphorylated variants of the encoded protein, which, in its non-phosphorylated state, coordinates processes such as cell division, apoptosis, CFTR splicing regulation, and microRNA biogenesis [3,8,16–19,22–26,28,34].
– The ***SORL1*** gene encodes a receptor involved in regulating the intracellular transport of proteins, including APP(amyloid precursor protein) [3,8,16–19,22–26,28,34].
– The ***SORT1*** gene is considered a risk factor because it encodes a receptor involved in the cleavage of amyloid precursor protein (APP) [3,8,16–19,22–26,28,34].
– The ***SNCA*** gene, also known as Synuclein A, contains the genetic information essential for the synthesis of SNCA peptides, which are major components in the structure of amyloid plaques and in the fibrillation of microtubules associated with TAU proteins. Other known functions of the gene include presynaptic signaling, membrane transport, dopamine release, and the reduction of responses to apoptotic stimuli [3,8,16–19,22–26,28,34].
– The ***TREM2*** gene plays a fundamental role in the formation of β-amyloid plaques, reducing their accumulation by activating a transmembrane receptor on microglia specific to these proteins. Alteration or inactivation of the gene leads to the excessive accumulation of β-amyloid plaques in the central nervous system. In its inactive form, the gene is associated with the onset of certain early-onset dementias, which follow an autosomal recessive inheritance pattern. The encoded membrane-bound protein, along with the TYRO kinase-binding protein, normally forms a receptor complex that modulates inflammatory processes and induces immune responses following signaling [3,8,16–19,22–26,28,34].

I. EOAD – autosomal-dominant or recessive, mendelian inheritance

Although the biological mechanisms are not fully elucidated and characterized, research has established direct correlations between the formation of neuritic plaques and alterations in the APP, presenilin 1(PSEN1), and presenilin 2(PSEN2) genes. The risk of developing AD is almost complete(100%) with mutations in either of the first two genes and approximately 95% with mutations in the third gene, with autosomal dominant familial transmission in most cases (Table I) [5,7,35].

AD caused by mutations in these three genes follows a monogenic, autosomal-dominant inheritance pattern, has a familial nature, and typically presents with early onset (before the age of 60-65, with rare cases being diagnosed in the third or fourth decade of life) (EOAD). It is estimated that approximately 1-5% of individuals globally diagnosed with AD have a familial form of EOAD with autosomal-dominant inheritance. Mutations in the APP, PSEN1, and PSEN2 genes account for 13% of all genetically determined EOAD cases, corresponding to 60% of the EOAD patient population (with 40% of these patients having no diagnosed relatives with AD) [4,6,23–25].

With around 330 known mutations in these three genes that follow mendelian inheritance, statistics show that 10-15% of EOAD cases are caused by mutations on chromosome 21, 30-70% by mutations on chromosome 14, and less than 5% by mutations on chromosome 1. Mendelian cases account for only approximately 10-15% of the total number of individuals diagnosed with EOAD [13,35].

Researchers have identified 23 autosomal-dominant mutations and one autosomal-recessive mutation in the APP gene (chromosome 21). Additionally, 185 possible mutations have been identified in the PSEN1 gene (chromosome 14), and 13 mutations in the PSEN2 gene (chromosome 1) [4,36].

The only exception among this vast group of mutations with strongly penetrant autosomal-dominant inheritance is PSEN2-N141I. However, all of these mutations lead to an increased molecular ratio of Aβ42 to Aβ40 (with the accumulation of the peptide Aβ42 promoting the conversion of monomers into oligomers, then into protofibrils, insoluble fibrils, and ultimately into dense or diffuse senile plaques), a characteristic that defines the phenotype of familial EOAD.

However, there is a ‚Swedish' mutation in the APP gene that deviates from the previously described pattern. Instead of selectively increasing Aβ42, this mutation elevates levels of all Aβ forms, leading to the rapid formation of

Table I. Early-onset familial Alzheimer's disease (EOAD) – genes and effects [4,36]

Gene	Protein	Chromosome	No. of mutations	Mode of inheritance	Molecular phenotype
APP	β-Amyloid precursor protein	21q21 21q21.3	24	Autosomal-dominant * one autosomal-recessive mutation: A673V	Increased Aβ42/Aβ40 ratio Overproduction of Aβ Intense Aβ aggregation
PSEN1	**Presenilin 1**	14q24 14q24.2	185	Autosomal-dominant	Increased Aβ42/Aβ40 ratio
PSEN2	**Presenilin 2**	1q31 1q42.13	14	Autosomal-dominant * PSEN2-N141I: does not follow autosomal-dominant inheritance	Increased Aβ42/Aβ40 ratio

aggregates due to amino acid substitutions within the Aβ domain [4,36].

APP – autosomal-dominant inheritance

The APP gene, located on chromosome 21, encodes the necessary information for the synthesis of surface receptors and primarily serves as a blueprint for producing the transmembrane amyloid precursor protein (APP), which is integral to the cell membrane. The enzymatic cleavage of APP by secretases results in the formation of distinct peptide fragments involved in neuronal adhesion and growth, as well as antibacterial, antifungal, and bactericidal processes. These fragments also play a role in axonal genesis under normal physiological conditions and in the modulation and activation of transcription in pathological cases. All mutations in the APP gene, except for one (autosomal-recessive), follow an autosomal-dominant inheritance pattern, akin to monogenic disorders.

APP – autosomal-recessive inheritance

In the specific case of the A673V mutation, the processing of the amyloid precursor protein (APP) is altered, leading to an overproduction of Aβ, which subsequently results in increased levels of protofibrils, fibrils, and eventually senile plaques. The A673V mutation in the APP gene involves a substitution at position 673 of the amino acid (alanine to valine) and induces familial EOAD only in homozygous descendants for the mutant gene. If the proband is the only one diagnosed with EOAD and the mutation is recessive, it implies that the parents were heterozygous, healthy carriers. This gene follows mendelian inheritance, with the phenotype manifesting only when two copies of the mutation are present (Figure 3) [37].

PSEN1

Mutations in the PSEN1 gene, located on chromosome 14, exhibit autosomal-dominant inheritance, akin to those in the APP gene.

Although the intact, unaltered PSEN1 gene contributes to skeletal development, embryonic brain formation, and cellular adhesion, it is also known to be involved in the Wnt and Notch signaling pathways and encodes the catalytic subunit of the γ-secretase enzyme [25].

The involvement of the presenilin genes PSEN1 and PSEN2 in the pathogenesis of familial EOAD stems from their association with the γ-secretase complex. This enzyme complex consists of four distinct proteins: Psen1, Psen2, Nicastrin, and Aph1. While Aph1 stabilizes the γ-secretase complex and Nicastrin functions as the enzyme's receptor, Psen1 contributes to the catalytic activity of the complex, and Psen2 is involved in its maturation. Mutations in these genes lead to an increased production of Aβ42 relative to Aβ40, with the elevated levels of Aβ42 contributing to neurodegenerative processes [38].

PSEN2

Similar to PSEN1 gene, the PSEN2 gene, located on chromosome 1, is involved in the synthesis of the catalytic subunit of γ-secretase. Additionally, PSEN2 plays a role in chromatin attachment to the nuclear membrane and is involved in intracellular signaling processes.

II. LOAD – multifactorial, non-mendelian inheritance

LOAD accounts for the majority of AD cases and typically begins after the age of 65. In contrast to EOAD, LOAD doesn't follow an autosomal-dominant, mendelian inheritance pattern. Instead, it is influenced by complex mechanisms that result from the ongoing interplay between genetic and environmental factors, making it difficult to pinpoint the specific genetic loci involved in its pathogenesis (Table II) [4].

Heritability for LOAD, a multifactorial disorder, ranges between 60% and 80%, with approximately 27% of this heritability attributable to forms associated with the APOE4 allele. Environmental factors contribute 20% to 40% to the overall risk profile [13,14].

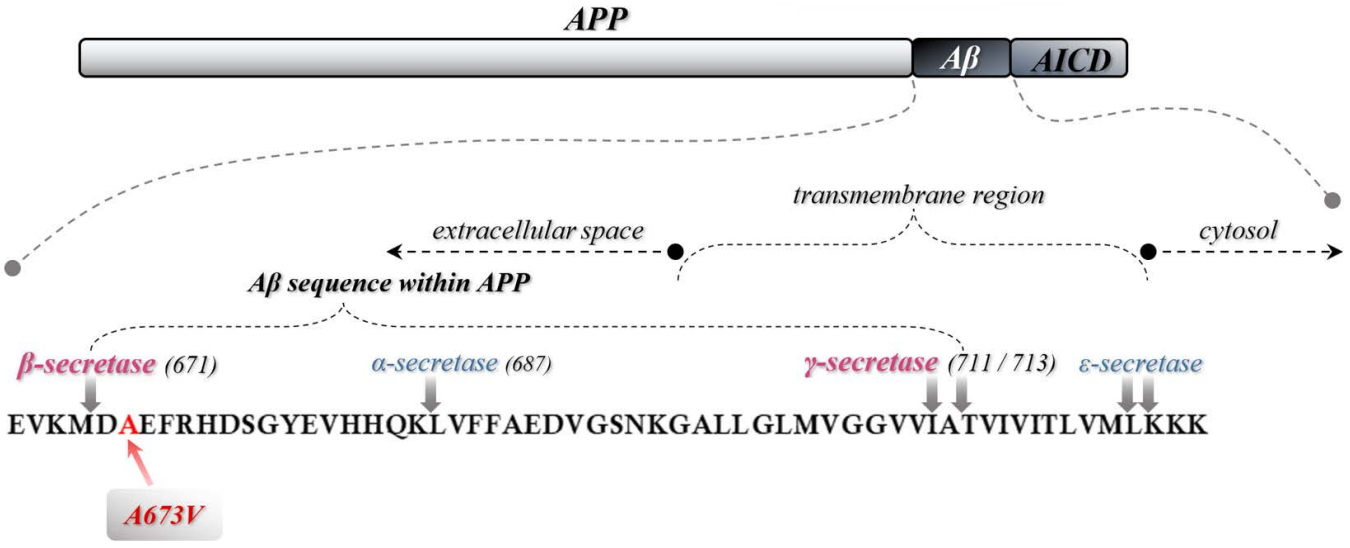

Fig. 3. Structure of APP and Secretase Cleavage Sites; A673V Substitution in APP with Autosomal Recessive Inheritance (red arrow) [21]

Table II. Anticipated pathogenic mechanisms in late-onset Alzheimer's disease (LOAD) [4,8]

Gene	Chromosome	Risk (%)	SNP	Molecular phenotype
CD33 Siglec 3	19q13.3 19q13.41	~ 10%	- rs3865444	Aβ degradation Innate immune responses Complement system Inflammatory response
APOE Apolipoprotein E	19q13.32	~ 400% -1500%	rs429358 rs7412	Aβ clearance Lipid metabolism
CLU Clusterin	8p21.1	~ 10%	rs11136000	Aβ clearance Innate immune responses Lipid/cholesterol metabolism
EPHA1	7q34	~ 10%		Cellular signaling Innate immunity
CR1	1q32.2	~ 15%	rs6656401	Aβ clearance Innate immune system Inflammatory response
BIN1	2q14.3	~ 15%	rs744373	Aβ clearance Cellular signaling Aβ production Endocytosis – synaptic vesicles
CD2AP	6p12.3	~ 10%		Cellular signaling
PICALM	11q14	~ 15%		Aβ clearance Aβ production Cellular signaling
ABCA7	19p13.3	~ 20%	rs3764650	Lipid metabolism Cellular signaling Inflammatory response Complement system
MS4A6A / MS4A4E	11q12.1 11q12.2	~ 10%	rs983392	Cellular signaling Immune system Inflammatory response Complement system
ATXN1	6p22.3	-		Aβ production
SORL1	11q24.1		rs11218343	Lipid transport Endocytosis: APP transport and metabolism
PICALM	11q14.2		rs3851179	Clathrin-mediated endocytosis
FERMT2	14q22.1		rs17125944	Angiogenesis TAU protein pathology
HLA-DRB5 / HLA DRB1	6p21.32		rs9271192	Immune system response Inflammation
EPHA1	7q35		rs11771145	Endosomal vesicles Immune system Inflammatory response Complement system
PTK2B	8p21.2		rs28834970	Synaptic functions in the hippocampus Cellular migration
CASS4	20q13.31		rs7274581	TAU pathology Axonal transport APP pathology Cytoskeletal functions
CD2AP	6p12.3		rs9349407	Cytokine receptor and endocytosis
INPP5D	2q37.1		rs35349669	APP metabolism Immune system response Inflammation
MEF2C	5q14.3		rs190982	Immune system response Inflammation Synaptic functions in the hippocampus
ZCWPW1	7q22.1		rs9349407	Epigenetic regulation
CELF1	11p11.2		rs10838725	Axonal transport Cytoskeletal functions

APOE

Among the broad spectrum of genes identified in studies of patients diagnosed with LOAD, the ε4 allele of the APOE gene, located at position 13 on the long arm of chromosome 19(19q13.32), is widely recognized in the scientific community as a significant risk factor [39,40].

Apolipoprotein E, involved at the molecular level in the transport processes of sterols and lipids through the circulatory and lymphatic systems, in the internalization of lipoproteins, the delivery of cholesterol within the brain structures, and in the catabolism of lipoprotein components with high triglyceride content, serving as a ligand for the LDL receptor, is encoded by the APOE gene (comprising 3 introns and 4 exons), which is located on chromosome 19, on the long arm(q) at position 13 [25].

An essential characteristic of the APOE gene is its polymorphism, which includes three distinct allelic types: ε4, ε3, and ε2. The combinations of these alleles result in six genotypic variants: APOE ε2/ε4, APOE ε2/ε3, APOE ε2/ε2, APOE ε3/ε4, APOE ε3/ε3, and APOE ε4/ε4 [7,20,40].

The distinction among the three APOE alleles is due to the specific combination of amino acids (Cys = Cysteine; Arg = Arginine) at positions 158 and 112: the ε2 allele has Cys112 and Cys158; the ε3 allele features Cys112 and Arg158; and the ε4 allele contains Arg112 and Arg158 [4,41].

However, the most studied alleles are ε2 and ε4, with the former being considered "protective" and the latter classified as "causative, or risk-associated." In AD, the ε4 isoform disrupts lipid metabolism, exhibits increased instability, and contributes to the formation of senile plaques and neurofibrillary tangles. Mutations in the APOE gene irreversibly affect the clearance of VLDL remnants and chylomicrons [4,23–25,40].

Another essential mechanism in the initiation of neurodegeneration in homozygous or heterozygous carriers of the ε4 allele is the accumulation of malondialdehyde and hydroxynonenal, leading to intense, heightened oxidative stress due to the diminished antioxidant function following the loss of cysteine residues.

The ε4 allele is involved in increasing neurotoxicity (induces and exacerbates neurocognitive deficits), which, along with enhanced oxidative stress, induces functional impairment of mitochondria (mitochondrial dysfunction) and is associated with various inflammatory mechanisms, vacuolar sorting proteins, metalloproteins, and processes such as TAU protein phosphorylation, nitric oxide synthesis, glucose or insulin metabolism, and neuronal development [25].

The presence of interneuronal APOE4 leads to synaptic loss, a process driven by the enhanced accumulation of Aβ, with the isoform being co-localized with oligomers. In the bloodstream, APOE4 acts as a carrier for Aβ peptides, facilitating their removal from the brain.

Studies have shown that asymptomatic individuals who carry the risk allele, though not diagnosed with AD, are more likely to have a positive result on amyloid PET scans and exhibit lower glucose metabolism compared to those with the disease(AD) [14].

The increased risk of developing LOAD is associated with the ε4 allele of the apolipoprotein E (APOE) gene, located on the long arm of chromosome 19, in 20-29% of cases. Thus, the likelihood of initiating neurodegenerative processes specific to LOAD is increased by approximately 2, 3, or 4 times for individuals with the APOE ε3/ε4 genotype (heterozygous) compared to the general empirical risk, which equates to about 10.4%. According to a study published in 2012 by Goldman J.S., 41% of patients with AD possess the APOE ε3/ε4 genotype, whereas only 21% of the healthy control group exhibits this combination of the two alleles. The same study establishes that although the presence of a single ε4 allele heightens the associated risks, 50% of carriers will not develop AD during their lifetime. Consequently, the detection of this allele during genotyping is not sufficient for a definitive predictive assessment.

Simultaneously, research reveals that the risk of developing LOAD increases approximately 8, 10, 12, 15, or 20 times for individuals who are homozygous for the ε4 allele (APOE ε4/ε4 genotype), with this risk being notably higher among women. The effects of risk factors and susceptibility genes are additive. According to the aforementioned study, 13% of individuals diagnosed with AD carry two copies of the ε4 allele (homozygous for ε4), whereas this genotype is present in less than 1% of the healthy control group (individuals not diagnosed with AD) [3,4,14,15,22–24].

Conclusions

AD is unequivocally characterized by a complex etiology involving the accumulation of neurofibrillary tangles and senile plaques, neurotrophin depletion, cerebral atrophy, and mitochondrial dysfunction. This pathology is influenced by the presence of allelic variants(APOE4), recessive(APP-A673V) or dominant autosomal mutations(PSEN1/2, APP). AD represents a multifactorial disorder arising from the intricate interplay between genetic (protective, causative, altered genes, mutations, risk alleles) and non-genetic demographic, physiological, behavioral, pathological, and environmental factors (chronic stress, smoking, chronic alcoholism, exposure to solvents, aluminium, and pesticides, associated diseases such as traumatic brain injury, diabetes, hypertension, obesity, hypercholesterolemia), or potentially from solely one of them. The progression from predisposition to the actual disease, however, is contingent upon the ongoing interaction and reinforcement of these two major categories of factors.

In the broader scientific consensus, biomedical research plays a crucial role in addressing the growing incidence of AD within the population. It is anticipated that future medicine will be redefined around the principles of individualized therapeutic strategies and personalized treatments. This approach emphasizes the identification and analysis of individual genetic predispositions and key factors that may drive the progression from vulnerability to the onset of the disease. The overarching aim is to monitor these factors throughout an individual's life, mitigate associated risks, and detect the condition in its early stages.

The multifaceted nature of neurodegenerative disorders, reflected in various hypotheses and forms such as senile and presenile dementias, Alzheimer's, mixed, and vascular types, is a direct consequence of a vast array of genetic mutations and established causal links to diverse epigenetic and biochemical alterations. The study of the heterogeneity and complexity of these disorders, with a focus on implicated genes, biochemical and molecular changes, allelic variants, rare autosomal dominant or recessive mutations, and triggering factors, holds fundamental importance. The accumulation of knowledge, along with the discovery of new processes, details, and interactions, serves as a crucial step toward transforming these profoundly life-altering diseases into conditions that can be detected early and managed effectively, with their progression slowed or even

halted through the efforts of multidisciplinary medical teams. Within this framework, genetics plays a pivotal role and occupies a central position, crucial for both understanding individual genetic makeup—including inherited predispositions from the maternal and/or paternal line and the associated risk—and analysing gene expression in the context of developing and testing pharmacological products, formulating extracts, modulating treatments, and assessing the impact of bioactive compounds.

Thus, it becomes evident that a comprehensive, multidisciplinary approach is essential for understanding this multifaceted condition. This includes investigating the various mechanisms of genetic components, as well as identifying individuals with increased vulnerability due to autosomal-dominant genetic burden (particularly in cases of EOAD) or, though very rarely, autosomal-recessive or polygenic susceptibility (as seen in LOAD forms). Moreover, it is crucial to raise public awareness about this extensive spectrum of neurodegenerative disorders and emphasize the importance of regular preventive screenings and consulting healthcare providers upon the emergence of initial symptoms because AD progresses at varying rates and patients may present with either slowly evolving forms, characterized by multiple plateaus and periods of stagnation, or rapidly progressive and fulminant forms.

Authors' contribution

PDS (Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft;)

Conflict of interest

None to declare.

References

1. Breitner JCS. Clinical Genetics and Genetic Counseling in Alzheimer Disease. Ann Intern Med. 1991;115(8):601-606. doi:10.7326/0003-4819-601
2. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genetics in Medicine. 2011;13(6):597-605. doi:10.1097/GIM.0b013e31821d69b8
3. Barber RC. The genetics of Alzheimer's disease. Scientifica (Cairo). 2012;2012:1-14. doi:10.6064/2012/246210
4. Tanzi RE. The genetics of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(10). doi:10.1101/cshperspect.a006296
5. Bird TD. Genetic aspects of Alzheimer disease. Genetics in Medicine. 2008;10(4):231-239. doi:10.1097/GIM.0b013e31816b64dc
6. Bekris LM, Yu CE, Bird TD, Tsuang DW. Review article: Genetics of Alzheimer disease. J Geriatr Psychiatry Neurol. 2010;23(4):213-227. doi:10.1177/0891988710383571
7. Williamson J, Goldman J, Marder KS. Genetic aspects of alzheimer disease. Neurologist. 2009;15(2):80-86. doi:10.1097/NRL.0b013e318187e76b
8. Carmona S, Hardy J, Guerreiro R. The genetic landscape of Alzheimer disease. In: Handbook of Clinical Neurology. Vol 148. III. Elsevier B.V.; 2018:395-408. doi:10.1016/B978-0-444-64076-5.00026-0
9. Tudose C, Maniu M, Maniu C. GENETICĂ UMANĂ. Editura CORSON; 2000.
10. Covic M. Curs de Genetică Medicală. Institutul de Medicină şi Farmacie, Disciplina de Biologie si genetică medicală; 1981.
11. Covic M, Stefănescu D, Sandovici I. Genetică Medicală. Editura Polirom; 2004.
12. Covic M, Ştefănescu D, Sandovici I. Genetică Medicală. Polirom; 2017.
13. Reitz C, Rogaeva E, Beecham GW. Late-onset vs nonmendelian early-onset Alzheimer disease: A distinction without a difference? Neurol Genet. 2020;6(5). doi:10.1212/NXG.0000000000000512
14. Soria Lopez JA, González HM, Léger GC. Alzheimer's disease. In: Handbook of Clinical Neurology. Vol 167. Elsevier B.V.; 2019:231-255. doi:10.1016/B978-0-12-804766-8.00013-3
15. Scheltens P, Blennow K, Breteler MMB, et al. Alzheimer's disease. The Lancet. 2016;388(10043):505-517. doi:10.1016/S0140-6736(15)01124-1
16. American Psychiatric Association. DSM-5-TR.; 2022.
17. American Psychiatric Association. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS - FOURTH EDITION - DSM-IV-TR.; 2010.
18. American Psychiatric Association. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS FIFTH EDITION - DSM-5-TR. Vol V.; 2022.
19. Morley JE, Farr SA, Nguyen AD. Alzheimer Disease. Clin Geriatr Med. 2018;34(4):591-601. doi:10.1016/j.cger.2018.06.006
20. Turner RS. Alzheimer's disease. Semin Neurol. 2006;26(5):499-506. doi:10.1055/s-2006-951622
21. Tcw J, Goate AM. Genetics of β-Amyloid Precursor Protein in Alzheimer's Disease. Cold Spring Harb Perspect Med. 2017;7(6). doi:10.1101/cshperspect.a024539
22. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. The Lancet. 2021;397(10284):1577-1590. doi:10.1016/S0140-6736(20)32205-4
23. Goldman JS. Predictive genetic counseling for neurodegenerative diseases: Past, present, and future. Cold Spring Harb Perspect Med. 2020;10(7):1-15. doi:10.1101/cshperspect.a036525
24. Goldman JS. New approaches to genetic counseling and testing for alzheimer's disease and frontotemporal degeneration. Curr Neurol Neurosci Rep. 2012;12(5):502-510. doi:10.1007/s11910-012-0296-1
25. Calabrò M, Rinaldi C, Santoro G, Crisafulli C. The biological pathways of Alzheimer disease: a review. AIMS Neurosci. 2021;8(1):86-132. doi:10.3934/Neuroscience.2021005
26. Nicolas G, Zaréa A, Lacour M, et al. Assessment of Mendelian and risk-factor genes in Alzheimer disease: A prospective nationwide clinical utility study and recommendations for genetic screening. Genetics in Medicine. 2024;26(5). doi:10.1016/j.gim.2024.101082
27. Pavarini G, Hamdi L, Lorimer J, Singh I. Young people's moral attitudes and motivations towards direct-to-consumer genetic testing for inherited risk of Alzheimer disease. Eur J Med Genet. 2021;64(6). doi:10.1016/j.ejmg.2021.104180
28. Knopman DS, Amieva H, Petersen RC, et al. Alzheimer disease. Nat Rev Dis Primers. 2021;7(1). doi:10.1038/s41572-021-00269-y
29. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's and Dementia. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005
30. Rademakers R, Dermaut B, Peeters K, et al. Tau (MAPT) muta tion Arg406Trp presenting clinically with Alzheimer disease does not share a common founder in Western Europe. Hum Mutat. 2003;22:409-411.
31. Rademakers R, Corsmit E, Cruts M, et al. Linkage and association studies identify a novel locus for Alzheimer disease at 7q36 in a Dutch population-based sample. Am J Hum Genet. 2005;77:643-652.
32. Ostojic J, Elfgren C, Passant U, et al. The tau R406Wmuta tion causes progressive presenile dementiawithbitempo ral atrophy. Dement Geriatr Cogn Disord. 2004;17:298-301.
33. Frigerio C, Piscopo P, Calabrese E, et al. PEN-2 gene mutation in a familial Alzheimer's disease case. J Neurol . 2005;252:1033-1036.
34. Bennett DA, Yu L, Yang J, Klein HU, De Jager PL. Epigenomics of Alzheimer's Disease. In: Epigenomics of Alzheimer's Disease. Elsevier Inc.; 2017:227-278. doi:10.1016/B978-0-12-800802-7.00009-5
35. Bird TD. Alzheimer Disease Overview. GeneReviews. Published online 1998:1993-2023.
36. Blasco D, Roberts JS. Implications of Emerging Uses of Genetic Testing for Alzheimer's Disease. Journal of Prevention of Alzheimer's Disease. 2023;10(3):359-361. doi:10.14283/jpad.2023.46
37. Di Fede G, Catania M, Morbin M, et al. A recessive mutation in the APP gene with dominant-negative effect on amyloidogenesis. Science (1979). 2009;323(5920):1473-1477. doi:10.1126/science.1168979
38. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: Pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine. 2019;14:5541-5554. doi:10.2147/IJN.S200490
39. Hutton M, Hardy J. The presenilins and Alzheimer's disease. Hum Mol

Genet. 1997;6(10):1639-1646.
40. Rosenberg RN, Lambracht-Washington D, Yu G, Xia W. Genomics of Alzheimer disease: A review. JAMA Neurol. 2016;73(7):867-874. doi:10.1001/jamaneurol.2016.0301
41. Mahley RW, Rall SC. APOLIPOPROTEIN E: Far More Than a Lipid Transport Protein. Annu Rev Genomics Hum Genet. 2000;1(1):507-537. doi:10.1146/annurev.genom.1.1.507