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Decoding the Genetic Basis of Alzheimer's Disease: A Comprehensive Review of Key Causal and Risk Genes, Pathological Mechanisms, Convergent Pathways, and Emerging Therapeutic Targets

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Abstract: Alzheimer's disease (AD) is the leading cause of dementia worldwide, accounting for approximately 60–70% of all dementia cases. It is a progressive neurodegenerative disorder that results in memory loss, cognitive decline and functional impairment, and affects over 55 million individuals worldwide. The number of affected individuals is projected to reach 139 million by 2050, posing a substantial public health and socioeconomic burden. Pathologically, AD is defined by extracellular deposits of amyloid-β (Aβ) plaques and intracellular accumulation of hyperphosphorylated tau in the form of neurofibrillary tangles (NFTs). There is growing evidence that the pathogenesis of AD is multifactorial, involving genetic, molecular, and environmental factors. This review aims to give a comprehensive overview of the major genes and molecular pathways involved in the pathogenesis of AD, as well as recent advances in genome-wide association studies (GWAS) and emerging therapeutic strategies. The mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), presenilin 2 (PSEN2), and β-site amyloid precursor protein cleaving enzyme 1 (BACE1) are associated with early-onset familial AD, while late-onset AD is linked to several susceptibility genes identified by GWAS. The molecular mechanisms underlying AD pathogenesis and progression are discussed with respect to major AD-associated genes, such as microtubule-associated protein tau (MAPT), apolipoprotein E (APOE), triggering receptor expressed on myeloid cells 2 (TREM2), sortilin-related receptor 1 (SORL1), bridging integrator 1 (BIN1), phosphatidylinositol-binding clathrin assembly protein (PICALM), Clusterin (CLU), ATP-binding cassette subfamily A member 7 (ABCA7), complement receptor 1 (CR1), acetylcholinesterase (AChE), nuclear factor erythroid 2-related factor 2 (NRF2), and tumor necrosis factor (TNF). Current therapeutic strategies, including anti-amyloid immunotherapy, AChE inhibitors, tau-directed therapies, and emerging gene-targeted approaches, are also discussed. In addition, progress in multi-omics technologies, disease models using induced pluripotent stem cells (iPSC), gene editing with CRISPR-Cas9, and artificial intelligence (AI) analysis are likely to speed up the implementation of precision medicine for early diagnosis, risk prediction, and treatment of Alzheimer's disease.

Keywords: Alzheimer's disease, APP, Tau, TNF, AChE, NRF2, Convergent Pathways, GWAS.

Review Paper

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INTRODUCTION

Alzheimer's disease (AD), the most common cause of dementia, is a chronic and progressive neurodegenerative disease that causes progressive loss of memory, cognition, language and executive function, culminating in total dependency and death. Dementia is a clinical syndrome, defined as a progressive decline in cognitive function that impairs functioning in daily life, and is responsible for about 60-70% of all dementia cases

worldwide. Over 55 million people currently suffer from dementia worldwide and this figure is expected to rise to 139 million by 2050, which has a significant socioeconomic impact on patients, caregivers and healthcare systems [1-3].

Pathologically, AD is characterized by extracellular deposition of amyloid-β (Aβ) plaques and intracellular deposition of hyperphosphorylated tau as neurofibrillary tangles (NFTs), which result in synaptic dysfunction, neuroinflammation, and progressive neuronal loss. The amyloid cascade hypothesis has been the most widely accepted explanation for the pathogenesis of AD for many years, but recent studies have suggested that the disease is a complex process involving several pathogenic pathways. These mechanisms are linked to each other, such as oxidative stress, mitochondrial dysfunction, neuroinflammation, protein clearance defects, endosomal trafficking defects, lipid dysregulation, cholinergic dysfunction, and synaptic impairment, which leads to progressive neurodegeneration and cognitive decline [4-6]. The main pathological mechanisms, genetic risk factors and disease course of Alzheimer's disease are summarized in (Figure 1).

An individual's susceptibility to Alzheimer's disease is a major factor that is determined by genetics. Early onset familial Alzheimer's disease (EOFAD) is caused by rare pathogenic mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes, while late onset Alzheimer's disease (LOAD) is associated with several susceptibility genes identified by genome wide association studies (GWAS). The genes involved in Alzheimer's disease are involved in critical biological processes such as amyloid processing, tau pathology, neuroinflammation, oxidative stress, cholinergic neurotransmission, lipid metabolism, endosomal trafficking, autophagy, and synaptic function, indicating the complex genetic architecture of Alzheimer's disease [7-9].

This review aims to give a comprehensive overview of the major genes and molecular mechanisms involved in Alzheimer's disease, focusing on their involvement in disease pathogenesis and progression. It also reviews recent progress in genome-wide association studies (GWAS), current therapeutic strategies, new gene-targeted interventions, and precision medicine approaches that may enhance early diagnosis, prevention, and treatment of Alzheimer's disease.

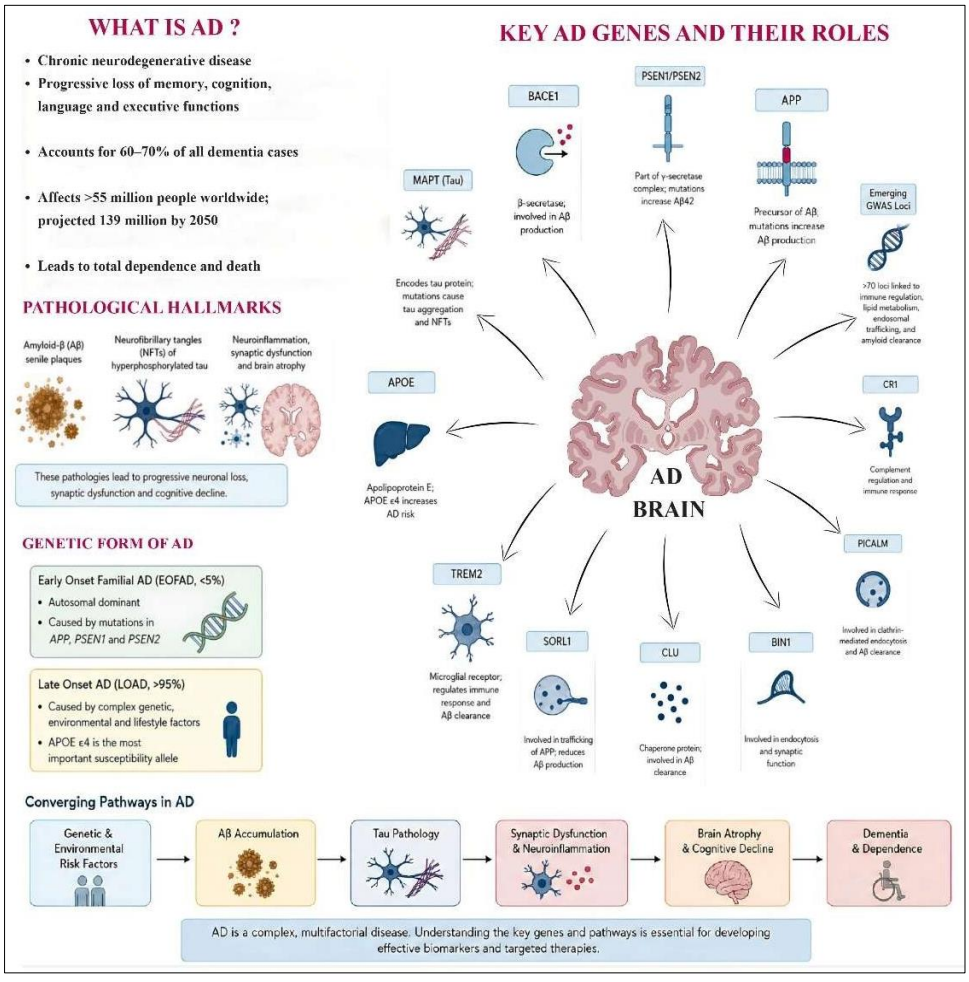

Figure 1: Overview of Alzheimer's disease Pathogenesis, Genetic Factors, and Disease Progression

1. The Molecular and Cellular Mechanisms Underlying Alzheimer's Disease

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder that is a result of complex genetic, molecular and cellular mechanisms. While the extracellular deposition of amyloid-β (Aβ) plaques and the intracellular deposition of hyperphosphorylated tau as neurofibrillary tangles (NFTs) are the pathological hallmarks of AD [4-6], there is growing evidence that the progression of the disease is a result of multiple interconnected biological pathways, rather than a single pathogenic process [10, 11]. Together, these pathways cause neuronal homeostasis to be disrupted, impairing the communication between synapses, causing neuroinflammation and ultimately resulting in progressive neuronal degeneration and cognitive decline [6-11].

The last few years have seen significant progress in the understanding of the pathogenesis of AD, with the identification of many genes that contribute to susceptibility to and disease progression of AD [9-13]. These genes are involved in important pathological mechanisms such as amyloid processing, tau pathology, neuroinflammation, cholinergic dysfunction, oxidative stress, endosomal trafficking, lipid metabolism, and autophagic dysfunction [8-14]. These pathways do not work in isolation, but converge to form intricate molecular networks that drive the progression of disease and neurodegeneration [15].

The genes associated with AD include mainly APP, PSEN1, PSEN2 and BACE1, which are mainly involved in the amyloidogenic processing and production of amyloid-β [6-17]. MAPT is a key player in tau pathology [18], while TNF and TREM2 control neuroinflammatory responses [11,19]. Moreover, AChE is involved in cholinergic dysfunction [20, 21], and NRF2 is involved in the antioxidant defence mechanisms of cells, protecting neurons from oxidative stress [22, 23]. In addition, susceptibility genes such as APOE, SORL1, BIN1, PICALM, CLU, ABCA7 and CR1 are involved in lipid metabolism, endosomal trafficking and autophagy dysfunction also will responsible for AD (Table 1) [24, 25].

Table 1: Major Pathological Mechanisms in Alzheimer's disease and Associated Genetic Factors

Pathological Process	Key Molecules/Genes	Major Consequences	References
Amyloid Cascade	APP, BACE1, PSEN1, PSEN2	Aβ42 accumulation, oligomer formation, amyloid plaque deposition	15–17
Tau Pathology	MAPT (Tau)	Hyperphosphorylation, PHF formation, neurofibrillary tangles	18–20
Neuroinflammation	TREM2, DAP12, IL-1β, TNF-α	Microglial activation, chronic inflammation, neuronal injury	21–23
Cholinergic Dysfunction	AChE	Acetylcholine depletion, impaired cholinergic neurotransmission, cognitive decline	20, 21
Oxidative Stress	NRF2, KEAP1	Reactive oxygen species accumulation, impaired antioxidant defence, neuronal damage	22, 23, 45
Endosomal Trafficking	SORL1, PICALM, BIN1	Altered APP sorting, impaired protein clearance	36–38
Lipid Metabolism	APOE, ABCA7, CLU	Cholesterol dysregulation, reduced Aβ clearance	36–38
Autophagy/Lysosomal Dysfunction	SORL1, BIN1, PICALM	Accumulation of Aβ, tau aggregates, damaged organelles	36–38

1.1 Amyloid Cascade Hypothesis

The amyloid cascade hypothesis is the most popular theory for the pathogenesis of Alzheimer's disease (AD). It suggests that abnormal processing of the amyloid precursor protein (APP) results in overproduction and accumulation of amyloid-β (Aβ) especially the aggregation-prone Aβ42 peptide. The amyloidogenic pathway involves sequential cleavage of APP by β-site amyloid precursor protein cleaving enzyme 1 (BACE1) and the γ-secretase complex (presenilin 1 (PSEN1) and presenilin 2 (PSEN2) to produce Aβ peptides. The amyloidogenic processing of APP is a complex process that requires the concerted activities of BACE1 and the γ-secretase complex, which results in the production of Aβ peptides and their aggregation into extracellular amyloid plaques (Figure 2). The deposition of Aβ42 triggers a series of pathological changes, such as synaptic dysfunction, neuroinflammation, tau hyperphosphorylation, neuronal loss, and gradual cognitive decline [4,15]. Despite the current understanding that AD is a multifactorial disorder with complex genetic, molecular and environmental factors, the amyloid dysregulation is believed to be one of the earliest molecular events that lead to the initiation and progression of the disease [6].

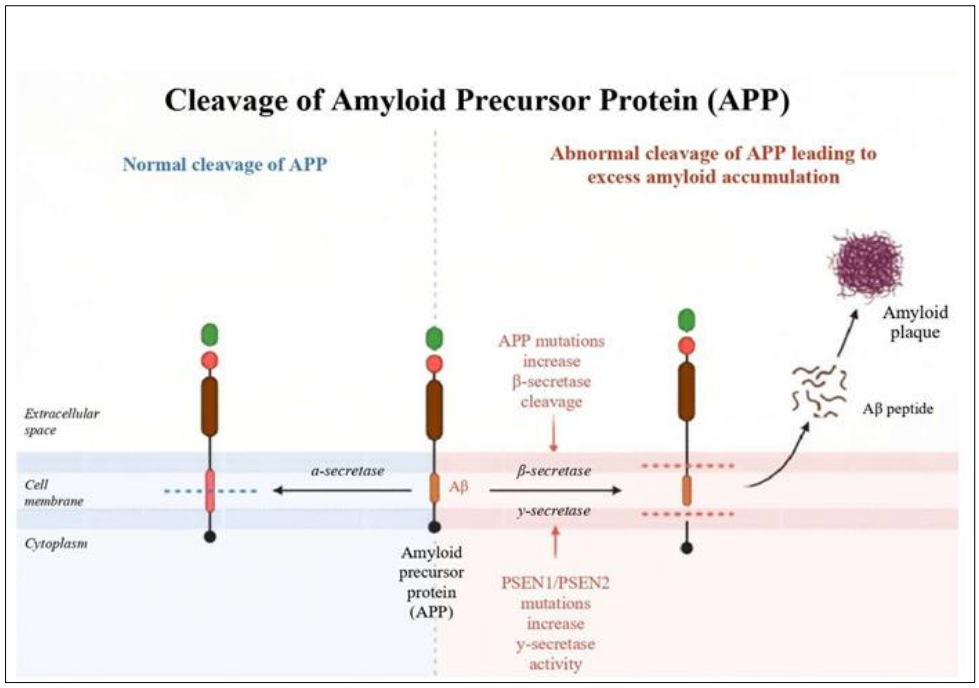

Figure 2: Amyloidogenic processing of APP, showing the involvement of BACE1, PSEN1 and PSEN2 in the generation of amyloid-β (Aβ) and plaque formation.

1.2. Tau Pathology

Another important pathological mechanism that has been proposed in the progression of Alzheimer's disease (AD) is the tau hypothesis. It suggests that abnormal phosphorylation of the tau protein results in the accumulation of intracellular neurofibrillary tangles (NFTs), which impair and disrupt neuronal function and degeneration. MAPT is a gene on chromosome 17 that encodes the tau protein, a key factor in stabilizing microtubules and controlling the transport of substances within the axon of neurons. In pathological states, hyperphosphorylation decreases tau-microtubule binding affinity, destabilizing the microtubules and leading to dysfunction of axonal transport. Hyperphosphorylation of MAPT-encoded tau causes tau to dissociate from microtubules, which results in paired helical filaments (PHFs) and eventually in neurofibrillary tangles (NFTs) that cause neuronal dysfunction and cognitive impairment (Figure 3). NFTs build up and spread, disrupting neuronal communication, impairing synaptic function and causing progressive neurodegeneration. While mutations in MAPT do not occur in a large proportion of cases of typical Alzheimer's disease, tau pathology is a strong marker for disease severity and cognitive decline, and therefore tau is an important biomarker and therapeutic target [14,35].

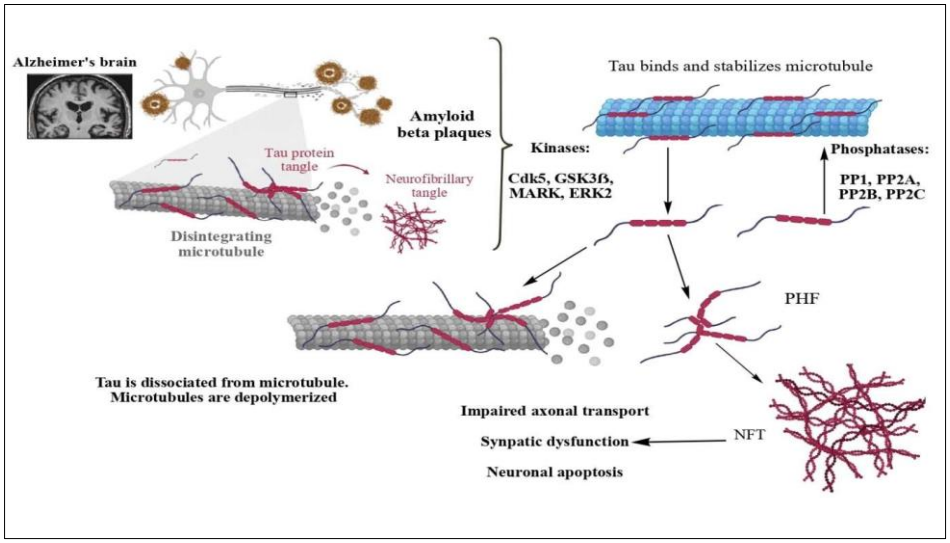

Figure 3: In Alzheimer's disease, MAPT gene encodes tau protein which is hyperphosphorylated and aggregated into paired helical filaments (PHFs), and neurofibrillary tangles (NFTs).

1.3. TNF Gene- Medicated Neuroinflammation in Alzheimer's Disease

Neuroinflammation plays a significant role in the development of Alzheimer's disease (AD) and is closely linked with the deposition of amyloid-β (Aβ) and the presence of tau pathology. Chronic neuroinflammation leads to the release of pro-inflammatory cytokines, chemokines, reactive oxygen species (ROS), and other inflammatory mediators, which can cause chronic microglia and astrocyte activation, leading to synaptic dysfunction, neuronal injury, and progressive cognitive decline [11,37]. These genes include TREM2, which controls microglial activation, phagocytosis, and amyloid clearance, and TNF, which encodes the proinflammatory cytokine TNF-α, which enhances inflammatory responses and neuronal damage. The neuroinflammatory process begins with activation of microglia by Aβ via TREM2 signaling, followed by the secretion of TNF-α and other pro-inflammatory cytokines, which results in chronic neuroinflammation and progressive neuronal damage (Figure 4). Impairment of these pathways will lead to decreased clearance of Aβ, chronic inflammatory responses and increased disease progression, making neuroinflammation a key therapeutic target in AD [18,39].

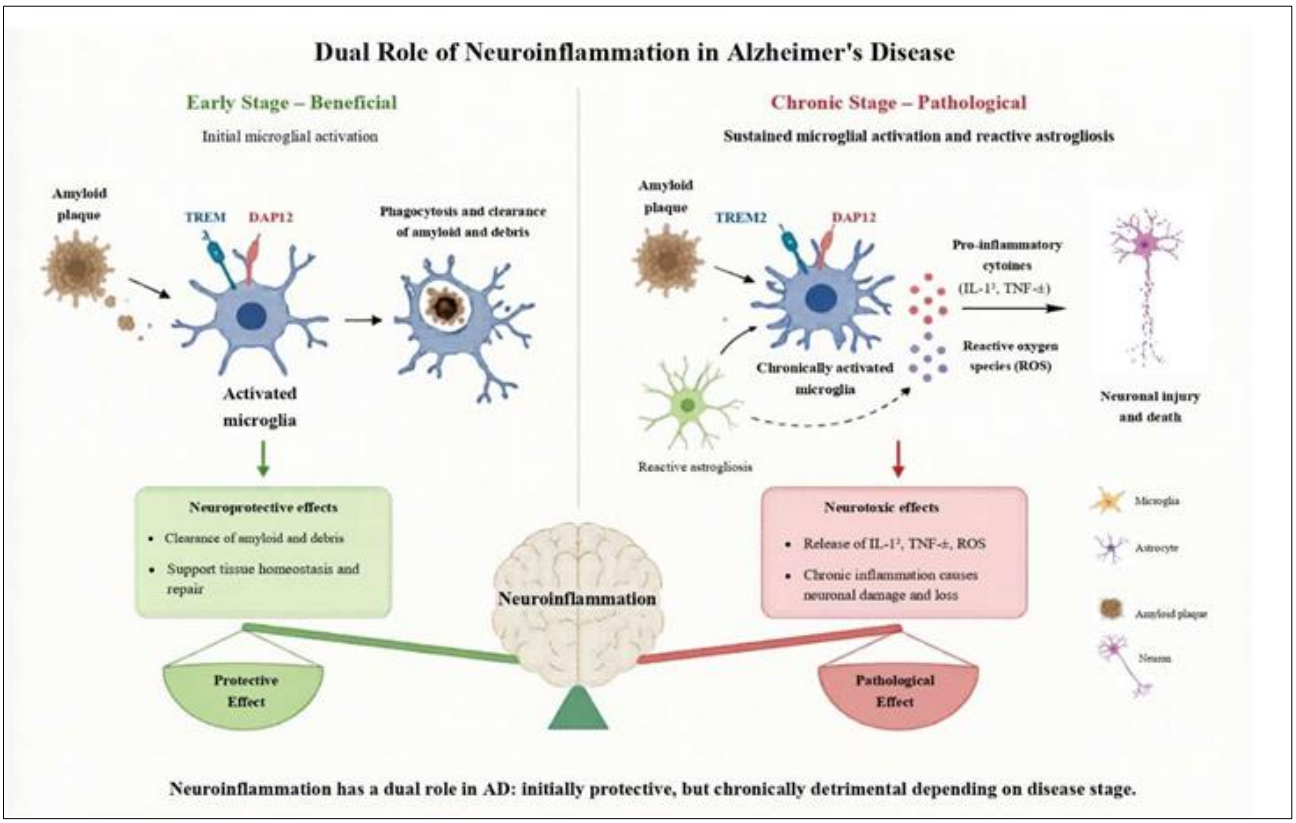

Figure 4: Convergence of Aβ- and tau-driven neuroinflammatory signaling, showing the activation of microglia by TREM2 and the release of cytokines by microglia via TNF-α resulting in chronic neuroinflammation in Alzheimer's disease.

1.4. AChE Gene and Cholinergic Deficit in Alzheimer's Disease

Cholinergic dysfunction is one of the earliest and most prominent neurochemical abnormalities in Alzheimer's disease (AD) and is a key factor in cognitive impairment and memory loss. According to the cholinergic hypothesis, the death of basal forebrain cholinergic neurons and the resulting reduction in acetylcholine (ACh) causes learning, memory, and attention deficits. The hydrolysis of ACh at cholinergic synapses is mediated by the enzyme acetylcholinesterase (AChE), and this enzyme is central to this process. Increased AChE activity leads to faster breakdown of ACh, leading to decreased cholinergic neurotransmission, synaptic dysfunction, and progressive cognitive decline. Besides its involvement in neurotransmitter metabolism, AChE has been demonstrated to promote the aggregation of amyloid-β (Aβ) which also contributes to the pathogenesis of Alzheimer's disease [20, 21]. Thus, AChE is still a relevant target for drug development and AChE inhibitors like donepezil, rivastigmine and galantamine are still the first choice of symptomatic drugs for Alzheimer's disease [40, 41].

1.5 NRF2 Gene and Oxidative Stress in Alzheimer's disease

One of the most important pathological mechanisms involved in the onset and development of Alzheimer's disease (AD) is oxidative stress. The brain

is very susceptible to oxidative damage, due to its high oxygen consumption, high lipid content and relatively low antioxidant defense system. The overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to the disruption of cellular redox homeostasis, which leads to lipid peroxidation, protein oxidation, mitochondrial dysfunction, DNA damage, and ultimately neuronal death [23,42]. These oxidative modifications also play a role in the accumulation of amyloid-β (Aβ), hyperphosphorylation of tau and progressive neurodegeneration.

Nuclear factor erythroid 2-related factor 2 (NRF2) signaling is an important mechanism for the defense of neurons against oxidative stress through the modulation of antioxidant and cytoprotective genes. In physiological conditions, NRF2 is bound to Kelch-like ECH-associated protein 1 (KEAP1) in the cytoplasm. Under oxidative stress, NRF2 releases from KEAP1 and enters the nucleus where it binds to antioxidant response elements (AREs) and induces the expression of genes that regulate cellular antioxidant defense, which in turn helps to maintain redox homeostasis and prevent oxidative damage to neurons [22,44]. Defective NRF2 signaling decreases cellular antioxidant capacity, increases oxidative damage and promotes disease progression. Thus, pharmacological activation of the NRF2 pathway has become an attractive therapeutic target to slow the progression of Alzheimer's disease [45].

1.6 Endosomal Trafficking, Lipid Metabolism, and Autophagic Dysfunction

Increasingly, endosomal trafficking, lipid metabolism, and autophagic dysfunction are emerging as key players in the pathogenesis of Alzheimer's disease (AD). Genome-wide association studies (GWAS) have revealed a number of susceptibility genes, such as apolipoprotein E (APOE), sortilin-related receptor 1 (SORL1), bridging integrator 1 (BIN1), phosphatidylinositol-binding clathrin assembly protein (PICALM), Clusterin (CLU), ATP-binding cassette subfamily A member 7 (ABCA7), and complement receptor 1 (CR1), which are involved in intracellular protein trafficking, lipid homeostasis, endosomal function, autophagy, and innate immune responses. Impaired function of these pathways leads to impaired clearance of amyloid-β (Aβ), abnormal protein accumulation, and neuronal degeneration [14,47]. These genes together create a molecular network that affects amyloid processing, tau pathology, synaptic integrity and disease progression.

Of these susceptibility genes, APOE is the most significant genetic risk factor for late-onset Alzheimer's disease (LOAD), specifically the APOE ε4 allele, which has been shown to have a negative effect on Aβ clearance, lipid transport, and amyloid deposition [38,48]. SORL1 is involved in the trafficking of APP between Golgi apparatus, endosomes and lysosomes, which helps to limit amyloidogenic processing, while BIN1 and PICALM are involved in clathrin-mediated endocytosis and vesicular trafficking that are crucial for normal neuronal function [19,24]. Furthermore, CLU, ABCA7 and CR1 are involved in lipid transport, phagocytic clearance of Aβ, complement activation, and innate immune regulation. The dysfunction of these genes can lead to disruption of cellular homeostasis and promote progressive neurodegeneration, making them targets of interest for disease modifying therapies [49, 50].

2. The Genetic Architecture of Alzheimer's disease

Genetic factors play a major role in the susceptibility, onset and progression of Alzheimer's disease (AD). In recent years, the molecular genetics and genome-wide association studies (GWAS) have led to identification of causative genes for early onset familial Alzheimer's disease (EOFAD) and susceptibility genes for late-onset Alzheimer's disease (LOAD). These genes are involved in various biological processes that are implicated in the initiation and progression of disease, such as amyloid processing, tau pathology, neuroinflammation, lipid metabolism, endosomal trafficking, protein clearance and synaptic function. (Table 2) presents the major genes associated with Alzheimer's disease, which includes the gene's name, the chromosome location, representative variants, disease association, main molecular mechanism, and risk association. The genetic features and pathological importance of these genes are presented in the next sections [7,12].

Table 2: Major Alzheimer's Disease-Associated Genes: Chromosomal Locations, Variants, and Molecular Mechanisms (Early- and Late-Onset Forms)

Gene	Chr	Mutation/Variant	Disease Association	Core Mechanism	Risk Association	Ref
APP	21q21.3	Swedish/London/Flemish	EOFAD	Aβ42 production	High	26–28
PSEN1	14q24.2	>300 mutations	EOFAD	γ-secretase alteration	High	16, 29, 30
PSEN2	1q42.13	N141I	EOFAD	Aβ42/Aβ40 increase	High	17, 31
BACE1	11q23.3	Expression variants	LOAD	β-secretase cleavage	Moderate	32, 33, 52
MAPT	17q21.31	H1 haplotype	LOAD	Tau aggregation	1.2–1.5	34, 35, 55

Gene	Chr	Mutation/Variant	Disease Association	Core Mechanism	Risk Association	Ref
APOE	19q13.32	ε4 allele	LOAD	Aβ clearance impairment	3–15	38, 56, 57
TREM2	6p21.1	R47H	LOAD	Microglial dysfunction	2–4.5	18, 39, 58
SORL1	11q24.1	LoF variants	LOAD	APP trafficking	2–5	19, 24, 49
CLU	8p21.1	rs11136000	LOAD	Aβ clearance	1.1–1.2	50, 60
BIN1	2q14.3	rs744373	LOAD	Tau propagation	1.15–1.25	61, 62
PICALM	11q14.2	rs3851179	LOAD	Endocytosis and BBB transport	1.1–1.2	59, 65, 66
CR1	1q32.2	rs3818361	LOAD	Complement mediated clearance	1.15–1.25	60, 68

2.1 Amyloid Precursor Protein (APP)

APP, located on chromosome 21q21.3, was the first gene associated with early-onset familial Alzheimer's disease (EOFAD) [26]. The mutations in the APP gene that are dominant in the family are associated with increased production and aggregation of Aβ, while the rare A673T mutation is protective [27, 28].

2.2 Presenilin 1 (PSEN1)

The γ-secretase catalytic subunit is encoded by PSEN1 on chromosome 14q24.2, and is the most commonly mutated gene in EOFAD, responsible for most of the autosomal dominant cases [16]. Mutations alter the Aβ42/Aβ40 ratio towards increased amyloid deposition [29], and are associated with early onset, rapid progression and significant clinical heterogeneity, which makes PSEN1 relevant for genetic counselling [7,51].

2.3 Presenilin 2 (PSEN2)

The other γ-secretase catalytic subunit, encoded by PSEN2 (1q42.13), has autosomal dominant mutations that are much less common than those of PSEN1 [17]. The mutations in PSEN2 have a lower penetrance and variable onset and clinical presentation, which adds to the clinical and genetic heterogeneity of FAD [31].

2.4 β-Site Amyloid Precursor Protein Cleaving Enzyme 1 (BACE1)

The gene encoding the rate-limiting enzyme that initiates amyloidogenic APP cleavage, BACE1, is located on chromosome 11q23.3. No direct causal mutations have been found, but high levels of BACE1 expression and activity are strongly associated with high production of Aβ, and BACE1 inhibitors have had limited clinical success [33,54].

There are several genetic susceptibility factors that contribute to the risk of Alzheimer's disease, but do not actually cause the disease, and these factors are involved in late onset Alzheimer's disease (LOAD). These genes are involved in a variety of biological processes such as lipid metabolism, innate immunity, endosomal trafficking, synaptic function and clearance of amyloid-β [8,12].

2.5 Microtubule-Associated Protein Tau (MAPT)

MAPT is located on chromosome 17q21.31 and codes for tau protein. While mutations in MAPT are uncommon in the typical Alzheimer's disease, the abnormal phosphorylation and aggregation of tau are tightly linked to disease progression and cognitive decline, and MAPT is an important biomarker and therapeutic target [35,55].

2.6 Apolipoprotein E (APOE)

APOE is the most important genetic risk factor for late-onset Alzheimer's disease, with the ε4 allele being a dose-dependent risk factor and the ε2 allele being a protective factor (19q13.32). In addition to lipid transport, APOE genotype influences the clearance of amyloid-β and the capacity of neuronal repair [38,57].

2.7 Triggering Receptor Expressed on Myeloid Cells 2 (TREM2)

TREM2 is expressed at high levels in microglia and is a regulator of innate immune responses in the CNS. Rare variants of TREM2 increase the risk of late-onset Alzheimer's disease by impairing microglial activation, decreasing amyloid-β clearance and increasing neuroinflammation [18,58].

2.8 Sortilin-Related Receptor 1 (SORL1)

The gene SORL1 is located on chromosome 11q24.1 and encodes a neuronal sorting receptor that controls the intracellular trafficking of APP. The SORL1 polymorphisms increase the risk of late-onset Alzheimer's disease by impairing protein sorting and enhancing amyloidogenic processing [19,24].

2.9 Bridging Integrator 1 (BIN1)

The second most important gene for late onset Alzheimer's disease is BIN1, which is located on chromosome 2q14.3. It controls membrane dynamics, endocytosis and tau-related neuronal processes, and its variants are always associated with increased disease susceptibility [25,49].

2.10 Phosphatidylinositol Binding Clathrin Assembly Protein (PICALM)

PICALM is located on chromosome 11q14.2 and is involved in clathrin-mediated endocytosis and intracellular vesicle trafficking. It has variants that impact the clearance of amyloid-β and synaptic function, which is associated with genetic susceptibility for late-onset Alzheimer's disease (LOAD) [50,59].

2.11 Clusterin (CLU)

The gene CLU, located on the short arm of chromosome 8 (8p21.1), codes for a molecular chaperone that plays a role in lipid transport, complement regulation, and clearance of amyloid-β. CLU variants are associated with protein homeostasis and neuroprotective function, and are associated with increased susceptibility to late onset Alzheimer's disease [60, 61].

2.12 ATP-Binding Cassette Subfamily A Member 7 (ABCA7) and Complement Receptor 1 (CR1)

ABCA7 is associated with lipid transport and microglial phagocytosis, and CR1 (1q32.2) is associated with complement-related immune responses. Mutations of both genes increase the risk of late onset Alzheimer's disease either by hindering the clearance of amyloid-β or by affecting innate immune function [62-64].

2.13 Additional GWAS-Identified Risk Genes

In recent years, many more genetic variants linked to late-onset Alzheimer's disease (LOAD) have been discovered in genome-wide association studies (GWAS). In addition to the susceptibility genes already mentioned, there are a number of other genes that have been linked to the susceptibility of Alzheimer's disease, such as CD33, CD2AP, EPHA1, MS4A6A, FERMT2, PTK2B, CASS4, HLA-DRB1, PLCG2, INPP5D, and SPI1. The major additional GWAS-identified risk genes and their biological functions such as innate immunity, microglial activation, endosomal trafficking, synaptic function, cytoskeletal organization and amyloid-β clearance, which reflects the multifactorial and complex genetic underpinning of Alzheimer's disease (Table 3) [65-67]. Future GWAS and large-scale meta-analysis will uncover more susceptibility loci, and these will help to shed light on disease mechanisms and enable precision medicine and targeted therapeutic strategies to be developed [68-70].

Table 3: Additional GWAS-Identified Alzheimer's disease Risk Genes

Gene	Chr	Top SNP	OR	Proposed Mechanism	Ref
ABCA7	19p13.3	rs3764650	1.15–1.25	Lipid transport, Aβ phagocytosis and clearance	68
CD33	19q13.41	rs3865444	1.10–1.20	Microglial inhibition, reduced Aβ clearance	69
MS4A4A	11q12.2	rs610932	1.08–1.15	Immune signalling and microglial function	70
EPHA1	7q34	rs11767557	1.10–1.15	Cell adhesion, synaptic signalling	71
CD2AP	6p12.3	rs9349407	1.10–1.20	Endocytosis and cytoskeletal organization	72
INPP5D	2q37.1	rs35349669	1.08–1.15	Microglial signalling and inflammation	73
MEF2C	5q14.3	rs190982	0.90–0.95	Neuronal survival and immune regulation	74
FERMT2	14q22.1	rs17125944	1.10–1.15	APP metabolism and synaptic maintenance	75
PLCG2	16q23.3	P522R	0.70–0.80	Protective microglial activation	76
ADAM10	15q21.3	Rare coding	Variable	α-secretase activity and APP processing	77
ABI3	17q21.32	S209F	1.40–1.50	Microglial activation and phagocytosis	78
PTK2B	8p21.2	rs28834970	1.10–1.20	Calcium signalling and synaptic plasticity	79
SLC24A4	14q32.12	rs10498633	1.05–1.10	Neuronal ion transport	80
NME8	7p14.1	rs2718058	1.05–1.10	Cellular transport and oxidative stress	81
HLA-DRB5/DRB1	6p21.32	rs9271192	1.10–1.20	Antigen presentation and immune regulation	

3. Convergent Pathological Pathways

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease in which several pathological mechanisms act together and in a connected way, and not independently. While amyloid-β (Aβ) deposition and tau pathology are the pathological hallmark of AD, recent evidence suggests that several other pathological processes, including neuroinflammation, oxidative stress, mitochondrial dysfunction, cholinergic impairment, lipid dysregulation, endosomal trafficking defects, and impaired protein clearance, all play a role in the progression of the disease. These interrelated pathological mechanisms converge and contribute to the impaired function of synapses, neuronal loss, and cognitive decline. These mechanisms interact to create a pathogenic cascade that is self-amplifying and drives disease progression and neurodegeneration [9,71]. Understanding these convergent mechanisms is essential for developing therapies that target multiple aspects of disease progression (Table 4, Figure 5) The knowledge of these interrelated molecular networks can be used as a solid basis for designing multi-target therapeutic strategies and precision medicine approaches for Alzheimer's disease [72, 73].

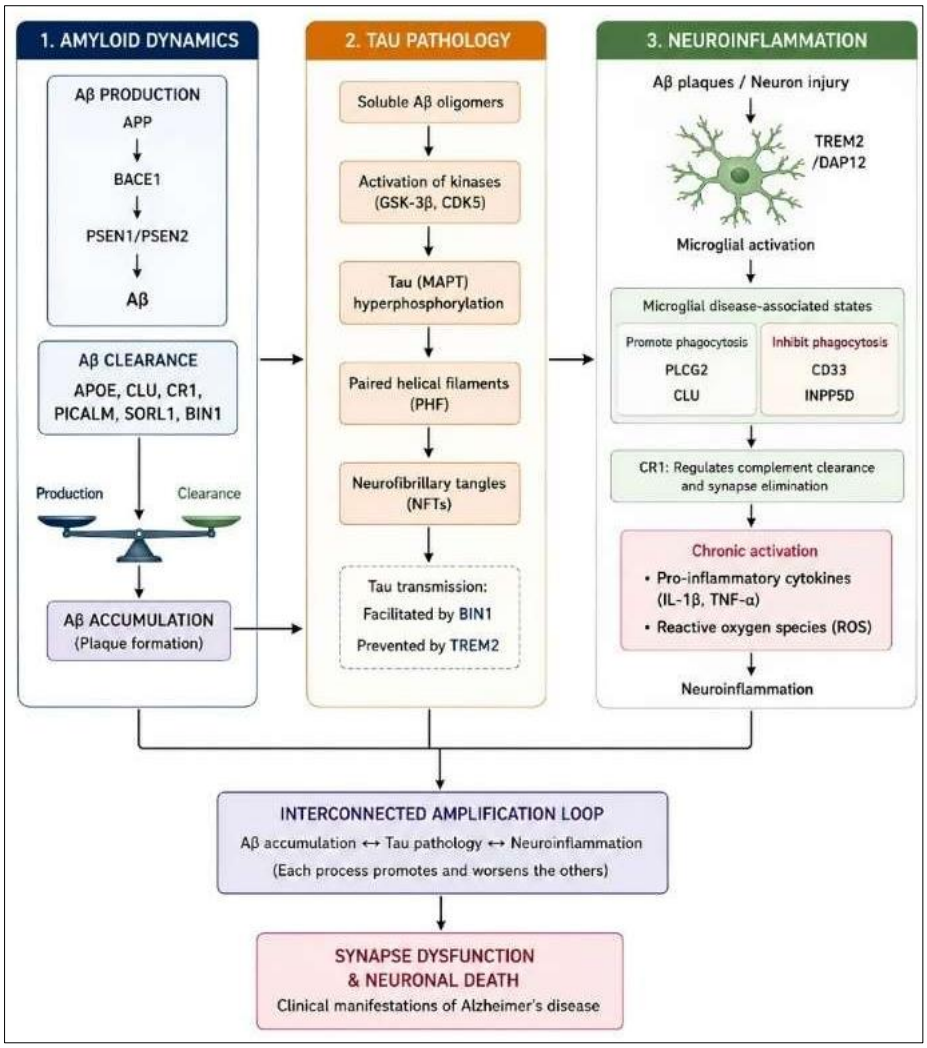

Figure 5: Convergent pathological pathways in Alzheimer's disease showing the interplay among amyloid dynamics, tau pathology, neuroinflammation, and associated genetic factors leading to synaptic dysfunction and neuronal degeneration

Table 4: Pathological pathways, genes associated and pathological significance in Alzheimer's disease

Pathway	Major Genes	Pathological Consequence	Ref
Amyloid Production & Clearance	APP, PSEN1, PSEN2, BACE1, APOE, CLU, CR1, PICALM, SORL1, BIN1	Increased Aβ42 production, impaired clearance, amyloid plaque formation	9, 38, 50, 83
Tau Hyperphosphorylation & Spreading	MAPT, BIN1, TREM2, APOE	Neurofibrillary tangles, tau propagation, neuronal loss	34, 35, 61, 62
Neuroinflammatory Cascade	TREM2, CR1, CD33, INPP5D, ABCA7, PLCG2, CLU	Chronic neuroinflammation, synaptic pruning, neuronal injury	11, 36, 67, 69
Endosomal Trafficking & Lipid Metabolism	SORL1, BIN1, PICALM, APOE, ABCA7, TREM2, CD2AP	Endosomal dysfunction, defective protein clearance, membrane abnormalities	14, 46, 49, 65

4. Therapeutic Implications

The molecular and genetic mechanisms involved in the pathogenesis of Alzheimer's disease (AD) have been advanced, leading to the development of therapeutic strategies aimed at several pathogenic pathways. The treatment options available today include acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine, galantamine), the N-methyl-D-aspartate

(NMDA) receptor antagonist memantine, and disease-modifying drugs (anti-amyloid monoclonal antibodies, lecanemab and donanemab). These treatments seek to enhance cognitive performance, decrease amyloid pathology, slow disease progression and improve patients' quality of life [6]. Although there have been recent developments, the existing treatments offer only limited clinical improvements, highlighting the need for targeted and multi-target therapies. (Table 5) highlights the key therapeutic strategies, their molecular targets, representative drugs, mechanisms of action and clinical applications in Alzheimer's disease [74].

Table 5: The major therapeutic strategies, molecular targets, representative drugs, and mechanisms of action in Alzheimer's disease

Drug/Therapy	Target	Trial Phase	Key Trial	Result/Status	Year
Lecanemab	APP/Aβ Protofibrils	Phase III	CLARITY-AD	FDA Approved	2023
Donanemab	Aβ Plaques	Phase III	TRAILBLAZER-ALZ 2	FDA Approved	2024
Aducanumab	Aβ Aggregates	Phase III	EMERGE/ENGAGE	Accelerated Approval	2021
Verubecestat	BACE1	Phase III	EPOCH	Failed	2018
Atabecestat	BACE1	Phase II	EARLY	Terminated	2018
Lanabecestat	BACE1	Phase III	AMARANTH/DAYBREAK	Failed	2018
Elenbecestat	BACE1	Phase III	MISSION AD	Terminated	2019
Umibecestat	BACE1	Phase II/III	GENERATION	Terminated	2019
Semorinemab	Tau	Phase II	LAURIET	Mixed Results	Ongoing (2026)
Gosuranemab	Tau	Phase II	TANGO	Failed Primary Endpoint	2021
IONIS-MAPTRx	MAPT ASO	Phase I/II	MAPTRx Study	Ongoing	Current (2026)
AL002	TREM2	Phase II	INVOKE-2	Ongoing	Current (2026)
GT005	APOE Pathway	Phase I/II	GT005 Trial	Ongoing	Current

4.1 Anti-amyloid Therapy

Therapeutic strategies have been developed based on the amyloid cascade hypothesis to decrease the production, aggregation, or deposition of amyloid-β (Aβ). Initial efforts aimed at targeting β-secretase (BACE1) and γ-secretase were not clinically successful due to poor efficacy and side effects. More recently, however, monoclonal antibodies that target aggregated Aβ have shown the potential to decrease cerebral amyloid plaques and to modestly slow cognitive decline in early AD patients [75, 76]. Clinically approved anti-amyloid antibodies (lecanemab and donanemab) are the first disease-modifying treatments for Alzheimer's disease, while aducanumab demonstrated proof of concept for amyloid-targeted immunotherapy, though there is still controversy about its clinical efficacy [77]. These advances highlight the therapeutic potential of early intervention and biomarker-guided treatment in Alzheimer's disease.

4.2 Anti-Tau Therapy

Anti-tau drugs have been identified as a promising disease-modifying approach to Alzheimer's disease, with a close relationship between tau pathology and cognitive decline. Therapeutic strategies are focused on blocking the hyperphosphorylation of tau, blocking tau aggregation, stabilizing the microtubules, and limiting the spread of pathological tau between neurons. A number of therapeutic agents have been studied in clinical trials, such as tau-targeting monoclonal antibodies (e.g., semorinemab, gosuranemab) and tau aggregation inhibitors (e.g., hydromethylthionine mesylate). While there are currently limited clinical effects, future treatment strategies are likely to be enhanced as the biology of tau continues to be elucidated and therapies are guided by biomarkers [78-80].

4.3 Anti-Inflammatory and Antioxidant Therapy

Neuroinflammation and oxidative stress are important players in the development of Alzheimer's disease and are potential therapeutic targets. The current therapeutic approaches focus on the inhibition of overactive microglial activation, the decrease of pro-inflammatory cytokines production and the improvement of the endogenous antioxidant defense mechanisms. Preclinical and clinical studies have shown several natural compounds and synthetic agents to have antioxidant and anti-inflammatory properties, such as curcumin, resveratrol, melatonin and N-acetylcysteine (NAC). Moreover, NRF2/KEAP1 pathway activation has been identified as a potential therapeutic target to mitigate oxidative damage and neuroinflammation, which helps to maintain neuronal function and slow disease progression [9,81]. These strategies have

demonstrated promising neuroprotective properties, but more extensive clinical studies are needed to determine their long-term effectiveness and safety in Alzheimer's disease patients.

4.4 Acetylcholinesterase (AChE) Inhibitor Therapy

The acetylcholinesterase (AChE) inhibitors continue to be the primary symptomatic therapy for patients with mild to moderate Alzheimer's disease. These agents block the enzyme responsible for the degradation of acetylcholine in the synaptic cleft, increasing the concentration of acetylcholine and improving cognitive function, memory and activities of daily living. The three approved AChE inhibitors (donepezil, rivastigmine, and galantamine) have shown modest, but consistent clinical benefits in slowing symptomatic decline, but cannot stop disease progression [81, 82]. Memantine is an NMDA receptor antagonist that can be used in combination with other drugs and may offer further benefit in patients with moderate to severe Alzheimer's disease [6]. Although effective, AChE inhibitors are frequently linked to gastrointestinal side effects such as nausea, vomiting and diarrhea, which can reduce long-term adherence to treatment [81].

4.5 Emerging Gene-Targeted and Precision Medicine

The advent of molecular genetics and genomics has led to rapid progress in the development of gene-targeted therapies and precision medicine for Alzheimer's disease (AD). The strategies involve harnessing technologies like antisense oligonucleotides (ASOs), RNA interference (RNAi), CRISPR-Cas9 genome editing, gene replacement strategies, and viral vector-mediated gene delivery to alter the course of disease. Furthermore, polygenic risk scores (PRS), biomarkers and genomic profiling are increasingly being investigated to identify high-risk individuals, to enable early diagnosis and to provide personalized therapeutic interventions [15-84]. While many of these strategies are still in pre-clinical or early clinical development, they are all promising avenues for precision medicine and could help to enhance the prevention and treatment of Alzheimer's disease in the future [14,85].

5. GWAS Studies and Their Contribution to the Understanding of Alzheimer's disease

The genetics of Alzheimer's disease (AD) has been significantly improved by the use of genome-wide association studies (GWAS), which have led to the discovery of many genetic variants linked to susceptibility for AD. These studies have contributed to an increased understanding of the complex genetic etiology of AD, identified new biological pathways that are important in pathogenesis, and enhanced understanding of the heritability of AD. Moreover, GWAS has revealed the significance of ancestral diversity and sex-specific genetic variation in the influence on AD risk, offering insights for genetic risk prediction and precision medicine [65, 66].

5.1 Heritability

Heritability is the percentage of disease risk that is due to genes in a population. Twin and family studies suggest that the heritability of late-onset Alzheimer's disease (LOAD) is in the range 60% to 80%, suggesting a significant genetic component in susceptibility to the disease. A large number of common genetic variants have been identified by genome-wide association studies (GWAS) that together account for a large proportion of this heritable risk. But a large proportion of the heritability of Alzheimer's disease has not been explained, known as "missing heritability," and this indicates that rare variants, gene-gene interactions, epigenetic changes, and environmental factors also play a role in the development of the disease [35,86].

5.2 Ancestral Diversity Gap

GWAS has identified a number of genetic risk loci associated with AD, but most studies have been performed in people of European descent, leaving a small number of studies in other populations. This ancestral diversity gap limits the ability to identify population-specific genetic variants, and decreases the ability to apply genetic risk prediction to a broad range of ethnic groups. The inclusion of multi-ancestry populations in GWAS is thus crucial to deepen the knowledge of the genetics of Alzheimer's disease and to develop precision medicine that is equitable [11,88].

5.3 Sex Differences

There are significant sex differences in genetic susceptibility, clinical presentation and progression of Alzheimer's disease. Alzheimer's disease is more common in women than in men, in part because women tend to live longer than men and are more likely to experience hormonal changes and genetic variations like the APOE ε4 allele that could increase the risk for women. It is crucial to include sex-specific analyses in GWAS to detect differential genetic effects and to inform the development of personalized prevention and therapeutic strategies [89-91].

6. CONCLUSION

Alzheimer's disease (AD) is a complex and multifactorial neurodegenerative disorder, which is caused by complex genetic, molecular and cellular mechanisms. The molecular genetics and genome-wide association studies (GWAS) have greatly contributed to the knowledge of the pathogenesis of AD, identifying genes that are important for the cause of the disease and genes that are important for susceptibility, and revealing the complex biological pathways involved in the disease. These findings have helped to develop specific therapeutic strategies and also offered novel opportunities for biomarker identification, early diagnosis, and precision medicine.

Future Directions

- This rapidly changing knowledge of the genetic and molecular mechanisms underlying

Alzheimer's disease will have a profound impact on future research and clinical care.

- The future will see more discoveries of new disease-associated pathways and therapeutic targets through, o Genome-wide association studies (GWAS) o Multi-omics technologies o Single-cell sequencing o Spatial transcriptomics.
- New therapeutic approaches such as gene editing, RNA-based therapeutics, antisense oligonucleotides and patient-derived stem cell models provide potential avenues for disease-modifying therapies. Treatment options in the future will move away from single-target therapies and towards multi-target and precision medicine approaches, which will target the complex pathological mechanisms of Alzheimer's disease.
- Ongoing multi-disciplinary cooperation and translation research will be crucial to translate the discoveries into the clinic, with the ultimate goal of improving the prevention, diagnosis, and treatment of Alzheimer's disease.

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