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Review Article

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Protective Genes Against Alzheimer's Disease: Case Review and Therapeutic Implications

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ABSTRACT

Alzheimer's disease (AD), a neurodegenerative disorder characterized by the accumulation of amyloid-beta plaques and tau tangles, shows cognitive decline. Recent genetic studies have identified over 30 variants that are resilient to AD pathology, offering new therapeutic opportunities. This review explores key protective mutations of *APOE3 Christchurch*, *RELN-COLBOS*, *FN1*, *APP A673T*, *BDNF Val66Met*, *SORL1*, *CR1*, *TREM2*, *PICALM*, and *INPP5 D* genes. These affect critical pathways, including lipid metabolism, synaptic function, tau regulation, and immune response. Potential treatments are discussed, including gene therapy and neuroprotective strategies, emphasizing a shift toward precision medicine focused on genetic resilience. By reviewing case studies and relevant literatures, the work explores the mechanisms by which these variants mitigate amyloid accumulation, tau pathology, neurodegeneration, and neuroinflammation, the key contributors to AD progression. Understanding these protective pathways offers critical insights into potential therapeutic applications, such as gene therapy, immune-modulating treatments, and personalized medicine approaches tailored to the individual's genetic profile. The findings highlight the potential to leverage genetic protection mechanisms to develop precision interventions for AD, offering new hope to prevent or delay disease onset and progression. These discoveries could transform future treatment strategies, shifting the focus from risk management to exploiting genetic resilience to combat AD.

Keywords: Alzheimer Disease; Cognitive Reserve; Genetic Variation

INTRODUCTION

Alzheimer's disease (AD), a leading cause of dementia, heavily impacts aging populations. Causal genes have been identified, such as *APP*, *PS1*, and *PS2*. Advances in gene sequencing technology, such as DNA microarray or next generation sequencing, and analysis by genome-wide association study, allow genes or their variants related to certain diseases to be identified. While much research has focused on risk genes, such as *APOE4*, recent discoveries have identified protective genetic variants that delay AD progression. Understanding these mechanisms opens new therapeutic avenues that are centered on enhancing neuroprotection and resilience.

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
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The reports of protective genetic variants arose mainly from case reports among the members with familial AD, or individuals with high-risk genes. To date, more than 30 protective variants have been identified. The studies in this review have been undertaken to understand the mechanism of these protective genes.

To conduct the literature review, we searched for "Alzheimer's disease," "protective genes," and "genetic resilience" in databases like PubMed and Google Scholar. Studies were screened for genetic variants that affect AD progression, focusing on those that showed promise in slowing disease pathology. Genes that were linked to faster cognitive decline, increased amyloid-beta (Aβ) accumulation, or enhanced tau pathology, were excluded.

Protective genes were selected based on strong experimental or clinical evidence, prioritizing those validated in multiple studies. We categorized them according to biological function and potential therapeutic relevance, ensuring that our review only included reliable findings.

This review categorizes these genes into 4 categories according to their mechanism: lipid metabolism, synaptic functions, tau pathology, and immune responses, the potential application of this knowledge to new therapeutic approaches then being discussed.

PROTECTIVE GENES AGAINST AD

Multiple genetic and environmental factors influence the complex neurodegenerative disorder that is AD. While many genetic variants increase susceptibility to AD, certain genes and mutations have been identified as protective, resisting disease progression through various biological pathways. Understanding these protective genetic factors provides crucial insights into the mechanisms of resilience against AD, and informs potential therapeutic strategies.

Protective genes are here categorized into 5 distinct functional groups, each of which contributes to AD resistance through different mechanisms:

1. Lipid metabolism: Genes that regulate cholesterol transport and lipid homeostasis, affecting Aβ accumulation and clearance.
2. Synaptic function and neuroplasticity: Genes that are involved in maintaining synaptic integrity and enhancing neuronal resilience.
3. Endosomal-lysosomal function and tau pathology: Genes that influence protein degradation pathways, including amyloid precursor protein (APP) processing and tau clearance.
4. Neuroinflammation and immune response: Genes that modulate the brain's immune system, reduce inflammatory damage, and enhance microglial-mediated Aβ clearance.
5. Combinatorial and systemic effects: Genetic alterations that affect mitochondrial function, alternative splicing (AS), and RNA interference, which contribute to overall neuroprotection.

We summarized the specific genetic mutations and their effects and roles in AD in **Table 1**.[1-34]

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Table 1. Summary of specific genetic mutations, and their effects and roles in AD

Gene/Variant	Effect	Role in AD	Ref.
APOE3 Christchurch	Delays onset of cognitive impairment	Reduced tau and Aβ pathology	1–3
RELN-COLBOS	Reduces tau phosphorylation	Protects against neurodegeneration	7,8
FN1 variant	Improves vascular integrity	Reduces Alzheimer's progression	30,31
BDNF	Decreases BDNF levels in APOE4 carriers	Reduces synaptic plasticity and neuronal survival	9,10
Maf1	Regulates transcription of synaptic genes	Impacts calcium homeostasis, synaptic plasticity, and cognitive functions	11,12
APP A673T (Icelandic)	Reduces Aβ production	Protective against Alzheimer's by shifting APP processing	14
APOE2	Increases lifespan and cognitive resilience	Protective against AD, associated with less Aβ accumulation	4
IL-6 gene	Examined SNPs; no direct association with AD, but a protective haplotype was observed	May confer protection via gene linkage or interaction mechanisms	22
LRP gene	*A216V polymorphism* negatively associated with AD, suggesting a weak protective effect	Weak protective effect but not sufficient to explain overall genetic risk	23
Mitochondrial gene alterations	Reduced nuclear and increased mitochondrial *OXPHOS* gene expression indicate mitochondrial imbalance	Mitochondrial dysfunction contributing to neurodegeneration in AD	32
PICALM	Regulates APP processing and Aβ production	Associated with AD risk in Caucasian populations	15–17
CLU	Forms complexes with Aβ to aid in clearance	Elevated levels linked to rapid disease progression	5
Butyrylcholinesterase K variant	K allele linked to slower cognitive decline in severe AD, relevant for treatment strategies	Modulates cognitive decline, influencing cholinesterase inhibitor strategies	24
VEGF-A	Involved in angiogenesis and neurogenesis	Epistatic interactions with APOE influence AD risk, highlighting vascular contributions to pathology	25
RAB10	Member of the RAB family involved in vesicular trafficking	Identified as a resilience locus, affects APP processing and Aβ metabolism, potentially influencing neurofibrillary tangles	18
P21 gene variation	RS1059234 T allele associated with lower AD risk and longer disease duration in an Italian cohort	Protective against AD and extends disease duration by modulating gene activity	29
APOE3-Jac	V236E substitution improves lipid binding, reduces insoluble APOE, and mitigates amyloid pathology	Decreases Aβ deposition, reduces microglial activation and inflammatory damage, and limits pathological APOE4 aggregation, offering a protective effect against AD and DLB	6
PDE4B	Inhibition prevents spatial memory deficits and reduces neuroinflammation	Highlights potential to improve cognitive outcomes through inflammation modulation	26
CXCR6	Mediates protective interactions between microglia and CD8+ T cells	Reduces Aβ plaque burden and neuroinflammation, providing immune-modulatory therapeutic potential	27
CTSH (rs2289702 T allele)	Decreases *CTSH* expression, enhancing Aβ clearance	Reduces AD risk by promoting microglial amyloid phagocytosis	19
PU.1	Reduced expression linked to delayed AD onset	Improves microglial function and reduces neuroinflammatory markers, offering insights into transcriptional regulation	20
IL1RL1 (rs1921622 A allele)	An allele associated with lower soluble ST2 levels, enhancing microglial activation	Reduces Aβ plaque load and improves cognitive outcomes, with gender and ethnic-specific variability	28
82-kDa ChAT	Upregulates genes involved in Aβ clearance	Promotes Aβ degradation, reduces neuroinflammation, and improves cognitive function	13
Alternative splicing events in microglia	Genes with altered splicing patterns in microglia	Impacts autophagy, actin reorganization, and synaptic plasticity, contributing to AD's pathogenesis	33
MiRNAs-associated genes	SNPs in 3'UTRs disrupt/create miRNAs response elements	Affects expression of genes critical in ADs, such as *GRN*, *TFCP2*, *PVRL2*, *ESR2*, *IDE*, *CDKN2A*, impacting amyloid and tau pathways	21
MiRNAs and RNA interference	Dysregulation of miRNAs affects several pathways	Aβ production and tau hyperphosphorylation pathways affected	34

APP: amyloid precursor protein, Aβ: amyloid-beta, AD: Alzheimer's disease, IL-6: interleukin 6, SNP: single-nucleotide polymorphism, DLB: dementia with Lewy bodies, miRNA: microRNA.

LIPID METABOLISM

APOE3 Christchurch (*APOE3ch*)

A unique case of autosomal dominant AD in a Colombian patient with the *PSEN1-E280A* mutation showed the unusually late onset in her seventies of mild cognitive impairment

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(MCI). Whole-exome sequencing identified homozygosity for the *APOE3ch* mutation, suggesting its protective effect. Despite extensive Aβ plaques, neuroimaging revealed limited tau pathology and minimal neurodegeneration.

In a humanized *APOE3ch* mouse model, researchers observed reduced Aβ deposition and decreased peri-amyloid tau pathology. This was linked to enhanced microglial response and greater tau aggregate degradation, along with reduced tau spread originating from decreased binding to heparan sulfate proteoglycans. These findings highlight *APOE3ch* as a potential mitigator of AD pathology through microglial activation and restricted tau propagation.[1-3]

APOE2

The *APOE2* variant offers significant protection against AD through both Aβ-dependent and independent mechanisms, including enhanced Aβ clearance, reduced aggregation, and improved synaptic and lipid metabolism. This variant is associated with slower cognitive decline, preserved brain structure, and increased longevity, but also presents risks for conditions like cerebral amyloid angiopathy. Therapeutically, *APOE*2 inspires strategies such as gene therapy, enhanced lipidation, and plasma-based interventions, though its associated risks necessitate cautious development.[4]

CLU rs11136000 variant

A meta-analysis of the rs11136000 polymorphism in the *CLU* gene was conducted, evaluating its association with AD across Asian and Caucasian populations. Both Asian and Caucasian cohorts confirmed the significant protective effect of the rs11136000 variant. The meta-analysis revealed consistent genetic risk patterns, with the allele model and dominant model showing strong associations with reduced AD risk. This suggests that the rs11136000 variant plays a protective role in AD pathology.[5]

APOE3-Jacksonville (*APOE3-Jac*) variant

The *APOE3-Jac* variant, which is characterized by a V236E substitution on the *APOE3* allele, is a protective genetic mutation that significantly reduces the risk of AD and dementia with Lewy bodies (DLB). This variant enhances APOE protein lipidation, improving brain lipid metabolism and reducing levels of insoluble APOE, which are associated with Aβ plaque deposition. Mouse models expressing *APOE3-Jac* show that amyloid deposition, microglial activation, and neuritic dystrophy around plaques are markedly reduced, demonstrating the variant's ability to mitigate amyloid-driven pathology and inflammatory damage. Additionally, the V236E substitution prevents the self-aggregation of APOE4, a major risk factor for AD and DLB, thereby indirectly reducing its pathological effects. Therapeutically, these findings suggest the potential of targeting APOE aggregation or enhancing APOE lipidation to replicate the protective effects of *APOE3-Jac*. Such strategies could benefit neuronal health by improving lipid transport and repair mechanisms, while reducing amyloid burden. Furthermore, these approaches hold particular promise for *APOE4* carriers, offering personalized interventions to address this high-risk population. By addressing both amyloid pathology and lipid metabolism, the *APOE3-Jac* variant provides a robust framework with which to develop innovative AD therapies.[6]

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SYNAPTIC FUNCTION AND NEUROPLASTICITY

Reelin-COLBOS

A male carrier of the PSEN1-E280A mutation, typically associated with early-onset AD (average onset at 44 years), remained cognitively healthy until age 67, but developed MCI at 70. He was heterozygous for the *RELN-H3447R* (*COLBOS*) variant, a gain-of-function mutation that enhances Dab1 activation and reduces tau phosphorylation. Despite extensive Aβ and tau pathology, his tau tangle burden was minimal in critical brain regions, preserving glucose metabolism and hippocampal volume.

In a mouse model, male mice carrying the *RELN-COLBOS* allele showed increased phosphorylated Dab1 levels, compared to females. These male mice also exhibited improvements in an abnormal limb-clasping behavior. However, the study faced limitations, such as small sample sizes, and a behavioral analysis that was limited to male mice. The *RELN-COLBOS* variant would appear to delay tau accumulation, protect synapses, and provide cognitive resilience in AD disease.[7,8]

BDNF and *APOE4*

A case study examined the interaction between *BDNF Met* and *APOE4* alleles in cognitively unimpaired adults, revealing that *BDNF Met* carriers with *APOE4* showed increased amyloid deposition and faster decline in glucose metabolism in brain areas that were affected by AD in common. Despite these changes, cognitive performance and hippocampal volume remained stable, potentially due to compensatory frontal brain activity in *BDNF Met* carriers; however, given the small sample size, this requires further validation.[9]

One study reinforces how *APOE4* and *BDNF Val66Met* polymorphisms interact to influence amyloid-related cognitive decline. *APOE4* carriers with high amyloid burden experienced accelerated cognitive decline, particularly in verbal episodic memory, a trend that the *BDNF Val66Met* variant worsened. These genetic interactions are crucial to understand AD progression and develop targeted preventive strategies.[10]

Maf1 gene

Maf1 regulates the transcription of the *Grin1* gene, which encodes the NMDAR1 protein, impacting calcium homeostasis and synaptic remodeling. In AD, increased *Maf1* expression leads to higher NMDAR1 levels, disrupting calcium balance while impairing synaptic function. In AD models, knockdown of *Maf1* has been shown to restore synaptic plasticity, reduce Aβ plaque, and improve cognitive performance.

Maf1 also influences dendritic morphogenesis and spine growth via the AKT-mTOR signaling pathway, modulated through PTEN expression. Reducing *Maf1* levels enhances dendritic growth and spine density by increasing phosphorylation in the AKT-mTOR pathway, while overexpression has the opposite effect. Thus, targeting *Maf1* may present a promising therapeutic approach for AD.[11,12]

82-kDa choline acetyltransferase (ChAT) isoform

This human-specific isoform of *ChAT* enhances cholinergic signaling and Aβ clearance. Its expression reduces neuroinflammation, and improves cognitive outcomes in AD mice. By upregulating genes involved in Aβ degradation, such as *ABCA1* and *insulin-degrading enzyme* (*IDE*), 82-kDa ChAT represents a novel target for cholinergic-based therapies in AD.[13]

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ENDOSOMAL-LYSOSOMAL FUNCTION AND TAU PATHOLOGY

APP A673T (Icelandic) case

By reducing Aβ production and aggregation, the *APP A673T* variant, discovered in Icelandic populations, has been shown to protect against AD, significantly lowering the risk of developing AD. The variant shifts APP processing toward a non-amyloidogenic pathway, resulting in reduced Aβ production and providing neuroprotection, even in the presence of amyloid plaques. This finding indicates the potential therapeutic avenue of targeting APP processing pathways to reduce AD risk.[14]

PICALM gene

Several studies explored how the AD-associated single-nucleotide polymorphism (SNP) *rs3851179*, near the *PICALM* gene, influences *PICALM* expression and splicing. *PICALM* is expressed primarily in micro vessels, and the protective *rs3851179G>A* allele was associated with a modest increase in *PICALM* expression. This upregulation in the microvasculature may enhance Aβ clearance across the blood-brain barrier (BBB), reducing AD risk. The study also discovered several *PICALM* splice variants, but only total *PICALM* expression was significantly associated with *rs3851179.*[15-17]

RAB10

The *RAB10* gene, part of the RAB family of small GTPases, has emerged as a critical resilience locus in AD, and offers insights into both disease mechanisms and therapeutic potential. A rare protective variant in the 3′−UTR of *RAB10 (rs142787485)* reduces *RAB10* gene expression, resulting in a lower Aβ 42/40 ratio, a key marker of AD pathology. Functionally, RAB10 is involved in intracellular trafficking pathways, including the retromer system, which regulates the processing of APP, and consequently, Aβ production. Phosphorylated RAB10 (pRAB10-Thr73) is observed in neurofibrillary tangles and dystrophic neurons near amyloid plaques, further linking RAB10 dysfunction to AD pathology. Therapeutically, inhibiting *RAB10* gene expression or activity has been shown to reduce Aβ production, making it a promising target for intervention. Potential strategies include the use of small molecules, antibodies, or antisense oligonucleotides, although challenges remain significant, such as delivery across the BBB. By highlighting the role of RAB10 in APP trafficking and Aβ pathology, this research underscores the importance of genetic resilience loci in guiding innovative therapeutic approaches, and in advancing our understanding of AD mechanisms.[18]

Cathepsin H (*CTSH*)

CTSH, a lysosomal protease, is associated with Aβ clearance. A protective T allele in the *CTSH* gene (*rs2289702*) reduces *CTSH* expression to enhance microglial Aβ phagocytosis. Genetic studies show that this variant decreases AD risk across populations, emphasizing its role in modulating microglial activity. Targeting *CTSH* could enhance amyloid clearance, without the problems of direct anti-Aβ strategies.[19]

PU.1 (SPI1)

PU.1, encoded by *SPI1*, regulates myeloid cell function, and is implicated in AD. Reduced expression of *PU.1* delays AD onset by improving microglial functions, such as phagocytosis and cytokine regulation. The *rs1057233* variant reduces *SPI1* expression, enhancing resilience to AD pathology. This highlights transcriptional regulation as a therapeutic target to modulate immune responses in neurodegenerative diseases.[20]

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MicroRNA (miRNA)-associated genes

Variants in the 3'UTRs of genes, such as *granulin (GRN)*, *transcription factor CP2 (TFCP2)*, *poliovirus receptor-related 2 (PVRL2)*, *estrogen receptor 2 (ESR2)*, *IDE*, and *cyclin-dependent kinase inhibitor 2A (CDKN2A)*, were studied for their interactions with miRNAs. The SNPs in these genes disrupt or create miRNA response elements (MREs) that affect the expression levels of genes critical in AD. For example, rs5848 in *GRN* creates an MRE for miR-185-5p, potentially impacting *GRN* regulation and influencing amyloid processing. These miRNA-related SNPs may modify the risk or progression of late-onset AD.[21]

NEUROINFLAMMATION AND IMMUNE RESPONSE

Interleukin 6 (*IL-6*) gene

Three SNPs in the promoter region of the *IL-6* gene were examined: *–174G/C*, *–572C/G*, and *–597G/A*. While no direct association between individual *IL-6* polymorphisms and AD was found, a protective effect was observed for the haplotype combining the –597A and –174G alleles. This effect was independent of the *APOE4* allele, suggesting a potential protective role in AD pathogenesis through gene linkage or interaction.[22]

Low-density lipoprotein receptor-related protein (*LRP*) gene

The *LRP* gene was investigated, a polymorphism in exon 6 (A216V) being examined to assess its association with AD. The *V216* allele was found to be negatively associated with AD in a French cohort, with an allelic frequency of 2.8% in controls, compared to 1.5% in AD cases. This suggests that the *V216* allele may have a weak protective effect against AD, although the authors note that by itself, this association cannot account for the entire genetic risk attributed to *LRP* in previous studies.[23]

Butyrylcholinesterase K variant

The impact of the butyrylcholinesterase *K* variant on the rate of cognitive decline in AD patients was investigated. The presence of the *K* allele was associated with a slower rate of cognitive decline in patients with severe AD (baseline Mini-Mental State Examination ≤8). This finding suggests a potential role for butyrylcholinesterase in moderating disease progression, and highlights its relevance in developing treatment strategies, such as cholinesterase inhibitors.[24]

Vascular endothelial growth factor A (*VEGF-A*) and related variants

VEGF-A is involved in angiogenesis, neurogenesis, and neuronal survival. Variants in *VEGF-A*-related genes were studied for their protective effects against AD. The study developed a predictive model for AD using SNPs in *APOE*, *LSR*, and *VEGF-A*. Epistatic interactions (gene-gene interactions) involving *VEGF-A* variants and *APOE* were found to significantly influence AD risk. For example, specific SNP interactions, such as *rs7043199* and *rs6993770*, showed protective effects, while the presence of the *APOE4* allele increased risk.[25]

Phosphodiesterase 4B (*PDE4B*)

PDE4B, a regulator of inflammation and neuronal function, plays a crucial role in AD pathology. A hypomorphic mutation in *PDE4B* gene prevents cognitive decline and glucose hypometabolism, despite no significant reduction in Aβ plaque load. RNA sequencing revealed that PDE4B influences inflammation-related genes, including *IDE*, which facilitates Aβ clearance. Its inhibition reduces pro-inflammatory cytokines like IFNγ and VEGF-A, suggesting a role in mitigating neuroinflammation and supporting cognitive resilience.[26]

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CXCR6

CXCR6 gene is expressed on CD8+ T cells, which in AD pathology are protective. CXCR6 + CD8 + T cells interact with microglia via CXCL16-CXCR6 signaling, promoting Aβ clearance while reducing plaque burden. Loss of CXCR6 exacerbates Aβ pathology, highlighting its importance in immune-mediated resilience to AD. This study introduces immune modulation as a potential avenue for AD therapy, targeting chemokine-receptor interactions to enhance protective T cell functions.[27]

Interleukin-1 receptor-like 1 (*IL1RL1*)

The *IL1RL1* gene encodes ST2, a receptor involved in IL-33-ST2 signaling that is critical for microglial activation. The *rs1921622* allele reduces soluble ST2 (sST2) levels, enhancing IL-33-mediated microglial responses, Aβ clearance, and cognitive resilience. The effects are pronounced in female *APOE4* carriers, and vary by ethnicity, suggesting tailored therapeutic approaches targeting sST2.[28]

P21 gene variation (Italian population)

The study examines the *P21* gene, focusing on 2 SNPs, *rs1801270* and *rs1059234. rs1801270* involves a C>A transversion at codon 31 in exon 2, resulting in a serine-to-arginine change (Ser>Arg). rs1059234, a C>T transition, is located 20 base pairs downstream from the stop codon of exon 3. The T allele of *rs1059234* was significantly associated with a lower risk of developing AD (odds ratio, 0.57; 95% confidence interval, 0.33–0.98; p=0.04). Additionally, patients carrying the *rs1059234* T allele had a longer disease duration of 4.3±2.5 years, compared to non-carriers at 3.3±2.1 years.[29]

Fibronectin 1 (*FN1*) variation

A study of cognitive resilience in elderly *APOE4* carriers identified a subset showing no cognitive decline, despite this high-risk genotype. Whole-genome sequencing revealed 510 rare coding variants, notably in extracellular matrix genes like *FN1.* Elevated fibronectin 1 levels were linked to delayed AD onset, suggesting a protective effect.

The *FN1* rs140926439 mutation appears to slow AD progression in *APOE4* carriers by reducing fibronectin deposition at the BBB. This leads to decreased gliosis, improved clearance of toxic proteins, reduced neuroinflammation, and enhanced vascular integrity, providing neuroprotection.[30,31]

COMBINATORIAL AND SYSTEMIC EFFECTS

Mitochondrial gene alterations

Changes in mitochondrial gene expression in blood samples from individuals with AD and MCI were assessed. The study found reduced expression of nuclear-encoded *Lunnon* (oxidative phosphorylation [*OXPHOS*]) genes in AD and MCI cases. Interestingly, mitochondrial-encoded *OXPHOS* genes showed increased expression in AD and MCI, suggesting imbalance between nuclear and mitochondrial genomes. This imbalance may compromise mitochondrial efficiency and increase reactive oxygen species, contributing to neurodegeneration in AD.[32]

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Alternative splicing events in microglia

Various genes underwent AS in microglia isolated from AD models. Key AS events affected genes involved in autophagy (e.g., *Eif2ak4*), actin cytoskeleton reorganization (e.g., *Mical1, Add1*), and synaptic plasticity (e.g., *Gpc2, Rbm3*). In AD, the splicing patterns changed significantly, with retained introns and skipped exons altering protein function. These modifications are linked to dysregulated synaptic signaling, autophagy, and actin dynamics, all of which are crucial for neuronal health, and contribute to AD pathogenesis.[33]

miRNAs and RNA interference

miRNAs are small, non-coding RNA molecules that post-transcriptionally regulate gene expression. They can target multiple mRNAs, making them potential multi-target therapeutic agents for AD. Dysregulation of miRNAs affects several pathways, including Aβ production and tau hyperphosphorylation. For example, miR-132 and miR-212 are involved in neuronal health and synaptic plasticity, while miR-124 and miR-146 are associated with neuroinflammation. The paper highlights miRNA-based therapies, such as miRNA mimics and inhibitors, as potential approaches to correct aberrant gene expression in AD.[34]

BIOLOGICAL PATHWAYS OF PROTECTION

AD is a multifactorial condition that shows complex interactions between biological pathways. As previously mentioned, certain genetic variants offer resilience against AD pathology by influencing key biological pathways. This section explores 4 potential mechanisms that are critical for AD pathophysiology: lipid metabolism, synaptic function and neuroplasticity, endosomal-lysosomal function and tau pathology, and neuroinflammation and immune response.

Lipid metabolism

The *APOE3ch* variant is associated with delayed onset of cognitive impairment and reduced tau and Aβ pathology, underscoring its role in lipid metabolism and neuroprotection.[1] Similarly, the *APOE3-Jac* variant, characterized by a V236E substitution, enhances lipid binding and reduces insoluble APOE, mitigating amyloid pathology.[6] The *APOE2* allele is protective against AD, as it is associated with reduced Aβ accumulation and enhanced cognitive resilience; in contrast, the *APOE4* allele exacerbates amyloid and tau pathology, significantly increasing AD risk. Other key players in lipid metabolism include the *CLU* rs11136000 variant, which aids in Aβ clearance by forming protective complexes.[5]

Synaptic function and neuroplasticity

Variants that influence synaptic function and neuroplasticity play a crucial role in AD resilience. The *RELN-COLBOS* variant reduces tau phosphorylation and protects synaptic structures, delaying the onset of neurodegeneration.[8] When interacting with *APOE4,* the *BDNF Val66Met* polymorphism is associated with reduced synaptic plasticity and neuronal survival.[10] *Maf1* regulates the transcription of genes involved in synaptic function, affecting plasticity and calcium homeostasis, while its knockdown restores synaptic health.[12] By improving synaptic signaling and neuronal health, the human-specific *82-kDa ChAT isoform* promotes Aβ clearance, reduces neuroinflammation, and enhances cognitive outcomes.[13]

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Endosomal-lysosomal function and tau pathology

Mutations that affect endosomal and lysosomal pathways influence tau pathology and Aβ metabolism. The *APP A673T* (*Icelandic*) variant shifts APP processing to a non-amyloidogenic pathway, significantly reducing Aβ production.[14] The *PICALM* rs3851179 SNP enhances Aβ clearance across the BBB,[17] while the *CTSH* rs2289702 T allele promotes microglial Aβ phagocytosis.[19] *RAB10*, involved in vesicular trafficking, regulates APP processing and Aβ metabolism, making it a key resilience locus.[18] Moreover, reduced expression of *PU.1 (SPI1)* improves lysosomal function in microglia, offering therapeutic insights.[20] Further, miRNA-associated genes, such as *IDE* and *GRN*, modulate amyloid and tau pathways through altered gene expression, while AS events in microglia affect autophagy and synaptic signaling.

Neuroinflammation and immune response

Neuroinflammation and immune pathways are critical to modulate AD progression. The *IL-6 gene* haplotype combining –597A and –174G alleles confers protection, suggesting anti-inflammatory effects.[22] *CXCR6*, expressed on CD8+ T cells, enhances interactions with microglia to promote Aβ clearance and reduce plaque burden.[27] The *IL1RL1* rs1921622 A allele enhances microglial activation through IL-33 signaling, improving Aβ clearance and cognitive outcomes, with pronounced effects in female *APOE4* carriers.[28] *VEGF-A*, involved in angiogenesis, interacts epistatically with *APOE* variants, influencing AD risk through vascular contributions.[25] *PDE4B* plays a dual role in inflammation and neuronal resilience, reducing neuroinflammatory markers and preventing cognitive decline.[26] The Butyrylcholinesterase K variant slows cognitive decline in severe AD by modulating inflammation and supporting synaptic health.[24] Finally, the *LRP A216V* polymorphism shows a weak protective effect by influencing Aβ metabolism, further highlighting the complexity of immune response pathways in AD resilience.[23]

We Summarized the key pathways and their associated genes in **Table 2**.[1-6,8,10-28]

DISCUSSION

The findings presented in this review emphasize the diverse biological pathways that influence AD progression, while highlighting numerous genetic and molecular mechanisms that are associated with resilience to the disease. This discussion categorizes their potential therapeutic implications into 6 domains of Pharmacological approaches, Gene therapy, Anti-inflammatory approaches, *APOE* targeting therapies, Targeting the BBB, and Combinatorial approaches, and outlines limitations and directions for future research.

Pharmacological approaches

Pharmacological strategies for AD have traditionally focused on targeting Aβ and tau pathology. Genetic insights provide novel drug targets, such as the *APP A673T* mutation,[14] which suggests shifting APP processing toward non-amyloidogenic pathways as a promising approach. Molecules that mimic the effects of *APOE3-Jac*, which reduces insoluble APOE and amyloid burden, could provide additional therapeutic avenues.[6] Inhibitors of *PDE4B* show promise in reducing neuroinflammation while preserving cognitive function.[26] Similarly, drugs targeting *CTSH* could enhance microglial Aβ clearance, addressing one of the central pathologies of AD.[19]

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Table 2. Summary of some of the key pathways and their associated genes

Pathway	Gene	Key function	Ref.
Lipid metabolism	*APOE3 Christchurch*	Delays onset of cognitive impairment, reduces tau and amyloid-beta pathology, enhances microglial activation.	1–3
	APOE2	Reduces amyloid-beta accumulation, enhances cognitive resilience, improves lipid metabolism, but increases risk of CAA.	4
	CLU (rs11136000 variant)	Aids in amyloid-beta clearance by forming protective complexes, reducing AD risk.	5
	APOE3-Jac	Enhances lipid binding, reduces insoluble APOE, mitigates amyloid pathology, and improves brain lipid metabolism.	6
Synaptic function and neuroplasticity	*RELN-COLBOS*	Reduces tau phosphorylation, protects synaptic structures, delays neurodegeneration, and provides cognitive resilience.	8
	BDNF Val66Met	Modulates synaptic plasticity and neuronal survival; exacerbates effects of APOE4 in AD pathology.	10
	Maf1	Regulates synaptic function and calcium homeostasis; knockdown improves synaptic plasticity and reduces amyloid-beta plaques.	11,12
	82-kDa ChAT isoform	Enhances cholinergic signaling, reduces neuroinflammation, and promotes amyloid-beta clearance, improving cognitive outcomes.	13
Endosomal-lysosomal function	*APP A67T*	Shifts APP processing toward a non-amyloidogenic pathway, reducing amyloid-beta production and aggregation.	14
	PICALM (rs3851179 SNP)	Enhances amyloid-beta clearance across the BBB, reducing AD risk.	15–17
	RAB10	Regulates APP processing and amyloid-beta metabolism via intracellular trafficking; rare protective variants reduce amyloid pathology.	18
	CTSH (rs2289702 T allele)	Promotes microglial amyloid-beta phagocytosis, enhancing clearance and reducing AD risk.	19
	PU.1 (SPI1)	Reduced expression improves lysosomal function in microglia, enhancing resilience to AD pathology.	20
	MicroRNA-associated genes	Modulate amyloid and tau pathways through altered gene expression, affecting amyloid processing and synaptic signaling.	21
Neuroinflammation and immune response	*IL-6*	Haplotype (−597A and −174G) confers protection by reducing inflammation and enhancing anti-inflammatory effects.	22
	LRP (A216V polymorphism)	Weak protective effect through influencing amyloid-beta metabolism.	23
	Butyrylcholinesterase K	Slows cognitive decline in severe AD by modulating inflammation and supporting synaptic health.	24
	VEGF-A	Influences AD risk through vascular contributions and angiogenesis, with epistatic interactions with APOE variants.	25
	PDE4B	Reduces neuroinflammatory markers, supports cognitive resilience, and mitigates inflammation-related neurodegeneration.	26
	CXCR6	Promotes interactions between CD8+ T cells and microglia, enhancing amyloid-beta clearance and reducing plaque burden.	27
	IL1RL1 (rs1921622 A allele)	Enhances microglial activation via IL-33 signaling, promoting amyloid-beta clearance and cognitive resilience, particularly in female *APOE4* carriers.	28

CAA: cerebral amyloid angiopathy, AD: Alzheimer's disease, APP: amyloid precursor protein, BBB: blood-brain barrier, IL-6: interleukin 6.

Gene therapy

Gene editing technologies like CRISPR-Cas9 provide opportunities to modulate AD-risk genes and introduce protective variants. For example, *RELN-COLBOS*,[8] *APOE2*,[4] and *APOE3-Jac*[6] could be introduced to high-risk individuals (e.g., *APOE4* carriers) to reduce Aβ and tau pathology. Knockdown of *Maf1* has been shown to restore synaptic plasticity and improve cognitive outcomes, making it a compelling target for gene therapy.[11,12] Additionally, manipulating miRNA-related pathways to regulate genes like *GRN* and *IDE* could help control Aβ production and tau phosphorylation.

Anti-inflammatory approaches

Neuroinflammation is a significant contributor to AD progression, and several genetic variants suggest potential anti-inflammatory therapies. Modulating the *CXCL16-CXCR6* axis to promote microglia-CD8+ T cell interactions could enhance Aβ clearance and reduce neuroinflammation.[27] Similarly, targeting the *IL-33-ST2* pathway (e.g., reducing sST2 via *IL1RL1 rs1921622* A allele) could enhance microglial activation and improve resilience in female *APOE4* carriers. The *IL-6 gene haplotype* also highlights how anti-inflammatory effects can mitigate AD pathology, offering pathways to develop therapies that are focused on cytokine regulation.[22]

APOE targeting therapies

Due to its dominant role in disease risk, *APOE* gene remains a central focus of AD research. *APOE3-Jac* demonstrates how improved APOE lipidation can mitigate amyloid-driven pathology and reduce neuroinflammation.[6] Therapeutic strategies could aim to replicate the effects of *APOE3-Jac* through small molecules, antibodies, or lipidation-enhancing compounds. Targeting APOE aggregation (particularly *APOE4*), or introducing protective alleles like *APOE2* via gene therapy,[4] also offers potential. These therapies would be particularly beneficial for *APOE4* carriers, who face significantly higher AD risk.

Targeting the BBB

The role of the BBB in AD pathology is underscored by the *PICALM rs3851179* variant, which enhances Aβ clearance via increased *PICALM* expression in microvessels.[17] Therapies that upregulate *PICALM* or improve vascular integrity through *FN1* variations could reduce gliosis and improve toxic protein clearance.[30] Similarly, variants in *VEGF-A* that contribute to vascular health provide opportunities to modulate angiogenesis and BBB integrity.[25] A therapeutic focus on the BBB could complement existing amyloid- and tau-targeting strategies, improving the delivery and effectiveness of treatments.

Combinatorial approaches

The multifactorial nature of AD necessitates combinatorial therapies that simultaneously target multiple pathways. For example, combining anti-inflammatory drugs (targeting *CXCR6*,[27] or IL-33) with lipid metabolism enhancers (targeting *APOE3-Jac*)[6] could address both inflammation and amyloid clearance. Gene therapy approaches, such as introducing protective alleles (e.g., *RELN-COLBOS*,[8] and *APOE2*),[4] while downregulating harmful genes (e.g., *Maf1*),[12] could offer synergistic benefits. Individuals carrying the *APOE4* allele with high amyloid load show faster cognitive decline, especially in verbal episodic memory, a deterioration further exacerbated by the *BDNF Val66Met* variant. These genetic interactions are key to understanding AD progression and designing targeted prevention strategies. Such personalized medicine approaches would tailor treatments to individual genetic profiles, maximizing therapeutic efficacy.

To better contextualize the genetic findings, we categorize the identified genes based on their level of replication and validation across studies. These categories (A, B, and C) help differentiate between well-established genes and those requiring further study. The following classification provides a clearer understanding of the reliability of these genetic associations in neurodegenerative research.

A. Well-established genes

These genes have been extensively studied and confirmed in multiple human cohorts, animal models, and genetic analyses. They are widely accepted as key contributors to AD risk or protection. The *APOE* gene, with its ε2, ε3, and ε4 alleles, remains the strongest genetic risk factor for AD, with ε4 significantly increasing susceptibility, and ε2 providing some protective effects. *PSEN1*, particularly the *E280A* mutation, is well-known for its role in autosomal dominant early-onset AD, while *PSEN2* mutations also contribute, albeit less frequently. Mutations in the *APP* gene, including variants like A673T and NL-G-F, drive amyloid pathology, which is central to AD progression.[14] *TREM2*, a gene implicated in microglial function, has also been established as an important factor in AD risk, affecting neuroinflammation and amyloid clearance.

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B. Genes replicated in multiple cohorts

These genes have been identified in multiple studies, often across different populations, but may require further validation in functional studies. *PICALM*, a gene involved in Aβ clearance, has been associated with Alzheimer's risk across numerous genetic studies.[16] *BDNF Val66Met*, a well-studied polymorphism, is linked to cognitive decline and neuroplasticity, with implications for Alzheimer's progression.[10] The *RELN-COLBOS*[8] and *H3447R* variants of *RELN* have shown protective effect against Alzheimer's, particularly in Colombian populations. *CLU*, specifically the rs11136000 variant,[5] has been identified in meta-analyses as an Alzheimer's risk factor in the Caucasian and Asian populations. Similarly, *FN1* rs140926439 and *COL6A2* have been linked to resilience against AD pathology in *APOE4* carriers. *CTSH* has emerged as a gene associated with reduced Alzheimer's risk through its effects on plasma Aβ levels, while *PU.1 (SPI1)* has been found to influence neuroinflammation and disease progression.[20]

The *IL1RL1* gene, particularly the rs1921622 variant in the ST2 signaling pathway, has been linked to lower AD risk in female *APOE4* carriers, showing consistent evidence in multiple cohorts.[28] BCHE-K interacts with *APOE4* to increase susceptibility to AD, making it an important factor in genetic risk studies. *Lrp1*, a gene central to amyloid clearance, has been replicated in various cohorts, strengthening its role in AD pathology. *ABCA1*, which regulates APOE lipidation, also plays a significant role in Aβ clearance. Lastly, *SST2* (*sST2*, *IL-33 pathway*) has been implicated in microglial responses to amyloid pathology, and has been observed in multiple genetic analyses.

C. Genes reported a few times

These genes have been associated with AD, but have only been reported in one study, and require replication before they can be considered strong candidates. *CXCR6* has been identified in a mouse model as a regulator of brain-resident CD8+ T cells in AD,[27] suggesting a potential role in immune responses. Although *VEGF-A* variants have been suggested to act as protective factors,[25] their role in larger cohorts remains unconfirmed. *Maf1* has been linked to neurodegenerative processes in Alzheimer's disease,[11] though its function is still unclear. *Grin1 (NMDAR1)*, a gene involved in synaptic plasticity, has been implicated in Alzheimer's-related cognitive decline, but more studies are needed to validate this link.

Other genes, such as *PDE4B*, have been found to protect against cognitive decline in Alzheimer's mouse models,[26] though human studies are lacking. Although *82-kDa ChAT*, a cholinergic marker, has been associated with reduced amyloid deposition,[13] the evidence remains limited. While *IL-6 (AG haplotype)* has been suggested as a protective factor against AD in a Brazilian case-control study,[22] it has not been replicated elsewhere. *RAB10*, identified through genetic database analysis, has been proposed as an Alzheimer's resilience locus, but before being widely accepted in the field, requires further validation.

While the classification above provides a structured understanding of the genetic landscape, it also highlights key challenges in the field. Many of the identified genes, particularly those in Categories B and C, require further replication and functional validation to establish their clinical relevance. Additionally, the complex interplay between genetic variants and environmental factors remains an area of ongoing investigation.

The following section outlines the major limitations of current research and suggests future directions to enhance our understanding of genetic contributions to neurodegenerative diseases.

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Limitations and future directions

While genetic studies provide critical insights into AD, before translating these findings into effective therapies, several challenges need to be addressed. Many protective variants, such as *APOE3 Christchurch*,[1] and *RELN-COLBOS*,[7] are rare, which limits their generalizability and applicability across diverse populations. The small sample sizes in both human and animal studies reduce statistical power, making replication in larger and more diverse cohorts essential.

Translating genetic insights into therapies presents additional hurdles, particularly in delivering treatments across the BBB, and mitigating potential immune responses or off-target effects. For example, gene-editing strategies may introduce unintended genetic modifications, while immunotherapies targeting protective pathways could trigger adverse inflammatory reactions. Furthermore, interventions designed to enhance protective mechanisms might need to be tailored to specific genetic backgrounds, complicating their clinical application. Future research should prioritize longitudinal studies to explore gene-environment interactions over time, as well as advances in precision medicine and gene-editing technologies. Integrating multi-omics data (e.g., transcriptomics, proteomics) with genetic findings could also help discover novel pathways and biomarkers for early diagnosis and treatment.

CONCLUSION

The genetic and molecular insights discussed highlight key pathways that contribute to resilience in AD, including lipid metabolism, synaptic plasticity, neuroinflammation, and BBB integrity. Variants, such as *APOE3 Christchurch*,[2] and *RELN-COLBOS*,[8] demonstrate potential mechanisms for delaying cognitive decline, while pathways that involve *PICALM*,[15] *CXCR6*,[27] and *VEGF-A*[25] emphasize the role of vascular and immune system health in AD progression.

These findings suggest a broader perspective on AD treatment that extends beyond amyloid and tau pathology to include protective mechanisms that could support cognitive resilience. However, significant challenges remain; these include the rarity of protective variants, the complexity of their interactions with other risk factors, and the difficulties in translating them into viable therapies. Future work should therefore focus on validating these findings in diverse populations, integrating multi-omics data, and developing combination approaches that address multiple aspects of AD pathology. By leveraging resilience pathways, it may be possible to develop more personalized and effective strategies to slow disease progression and improve patient outcomes.

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