The Role of Genetic Factors in Alzheimer's Disease Treatment

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Alzheimer's Disease (AD) is a chronic progressive neurodegenerative disorder characterized by progressive cognitive decline, memory loss and the presence of amyloid-β plaques and neurofibrillary tangles. A considerable amount of work has been done in the area of therapeutic development, but no treatment has been shown to halt progression; anti-amyloid antibodies modestly slow decline of the disease, and the majority of treatments are still mostly symptomatic. This review focuses on the genetic aspects of pathogenesis and treatment of AD and its relevance to precision medicine. The review includes the genetics of AD; highly penetrant mutations related to familial AD and susceptibility genes related to late-onset forms. It also emphasizes the role of pharmacogenomics in the research of interindividual variability in drug response, drug efficacy and drug adverse reactions. New gene therapies such as RNA interference and CRISPR/Cas9 gene editing are also considered. The review also includes a glimpse into the use of personalized medicine – genotype-directed clinical trials and companion diagnostics – to enhance treatment precision and patient stratification. There are still many challenges such as genetic heterogeneity, lack of predictive power and lack of translation to clinic, however. Progress in genetic understanding has greatly broadened knowledge of the mechanisms of AD and provided a new path for targeted therapeutic interventions but is still not yet ready for widespread implementation in clinical practice, needing to be validated, delivery systems enhanced and more complete therapeutic interventions developed. APOE ε4 predicts ARIA risk with anti-amyloid antibodies, but no genotype has been shown to predict treatment benefit.

Keywords: Alzheimer's Disease, Genetics, Pharmacogenomics, Personalized Medicine, Gene Therapy

Introduction

Alzheimer's disease, or AD, is one of the most widespread neurological disorders globally[1]. AD has an approximate heritability of 60 to 80 percent, which indicates a substantial genetic contribution to individual susceptibility, while its increasing global prevalence is majorly related to the aging population and increased life expectancy, which contribute to a larger number of individuals at risk of developing the disease[2]. It is also important to know that Alzheimer's is most common in adults above the age of 65, and roughly two-thirds of patients are female[3,4]. Alzheimer's disease and other dementias are expected to affect 152 million individuals worldwide by 2050 due to their increasing prevalence along with other neurological disorders[4].

AD is explained as the chronic impairment of acquired memory along with numerous cognitive defects in domains such as behavior alterations, language, and executive capacity. All of this leads to a gradual deterioration of personal volition[5]. Alzheimer's disease is distinguished histopathologically by two hallmark neuropathological features. Amyloid-beta peptide (Aβ) fibrils clump together outside the cells to form neuritic plaques, and there is also a buildup of abnormally phosphorylated Tau protein inside the cells, which leads to the formation of neurofibrillary tangles (NFTs) in the subcortical grey matter and cerebral cortex[6]. The Tau protein is a normal neuronal protein which plays a crucial role in maintaining the cytoskeleton network through the process of promoting microtubule assembly and stability[6]. In AD, the abnormal phosphorylation of the Tau protein reduces its ability to maintain the microtubule stability and causes its misfolding and aggregation into neurofibrillary tangles[6]. Pathological Tau can also be released from living neurons into extracellular space, wherein it may be taken up by closer neighboring cells and thus contribute to the propagation of Tau pathology[6]. This process may lead to neuronal dysfunction and injury, while the cellular damage and pathological tau can potentially activate microglial cells, which leads to the release of pro-inflammatory cytokines and contributing to neuroinflammation[6,7].

Current treatments for Alzheimer's disease primarily focus on the management of AD using cholinesterase inhibitors and memantine, which have limited cognitive benefits without halting the disorder's progression. Recent advances in the treatment of AD such as amyloid-targeting monoclonal antibodies aim to slow disease progression, despite the fact that their clinical benefits remain modest[8]. Furthermore, although there are numerous advances in healthcare, the exact causes or reasoning for AD are still unclear, which makes it difficult

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for scientists to develop appropriate treatments and preventive measures [9]. Moreover, as populations will start to age, the demand for care and treatment in cases of AD and other dementias is also projected to increase rapidly. This will lead to the increased burden of Alzheimer's globally; although current approaches to treat this disorder remain majorly symptomatic and fail to reduce the true impact of this neurodegenerative disorder.

The current treatments of AD are split into two categories, which are pharmacological and non-pharmacological [4]. The non-pharmacological therapeutics include personalised activities and enjoyable activities catered for the patients. It is important that these specific treatments can be effective in managing the behavioral and psychological symptoms of dementia [10,11]. However, despite these advantages, the real-world impact of these therapeutics remains limited due to practical and systematic constraints [12]. In contrast to this, pharmacological treatments such as antipsychotics, SSRIs and non-opioid analgesics remain largely limited by modest efficacy, and significant safety concerns which creates a notable gap between the clinical guidelines and real-world application of these forms of medications [13]. Overall, current treatments for AD and other dementias significantly limit their effectiveness in managing these neurodegenerative disorders. These drawbacks highlight the immediate need for effective treatment strategies for the disease's detection, therapy, mitigation and care. The goal of this review is to determine how genetic factors affect the various treatments of Alzheimer's disease.

Methodology

A literature review was conducted using Google Scholar, this was conducted in the months of January and February 2026 to identify relevant research on the genetic factors involved in Alzheimer's disease and their implications for treatment strategies development. The search terms included "Alzheimer's disease genetics," "*APOE,*" "polygenic risk score," "pharmacogenomics," "gene therapy," and "personalized medicine." Boolean operators such as AND and OR were used to combine key terms and refine the search process. Fifty articles were initially identified, of which fourteen were screened in greater detail on their relevance, depth of information along with alignment with the objectives of this review.

Articles were included only if they examined genetic factors associated with AD pathogenesis, disease risk, treatment response, gene therapy, pharmacogenomics or personalized medicine, and most importantly if they provided relevant experimental or clinical evidence. Articles with limited relevance to the genetic or therapeutic focus of the review were excluded. Additional relevant publications were identified through tracking the references of the selected articles. Both experimental model-based research and human clinical trials were considered.

The quality of the literature selected was assessed in a qualitative manner on the basis of reliability and depth of the published evidence, including the scientific credibility of the journal and the relevance of the study to the objectives of the review. No formal risk-of-bias assessment tools were used.

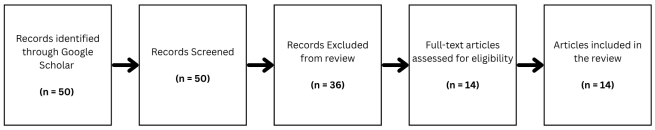


Figure. 1 PRISMA flow diagram of the literature search and study selection process

Genetic Factors in AD

Familial AD Genes

Approximately 2% of all occurrences of Alzheimer's disease are familial Alzheimer's disease (FAD), accounting for a rare form of the disease. FAD has a genetic basis, as it has been well-characterized and has a high degree of penetrance creating an increased opportunity to study the pathophysiology of the disease. Research has found three primary genes that are responsible for familial Alzheimer's disease [1]. The *amyloid precursor protein* (APP) gene, the presenilin-1 gene (*PSEN1*) and *presenilin-2* gene (*PSEN2*). These three genes have distinct roles in the amyloid pathway: *APP* encodes the precursor protein from which Aβ peptides are derived, whereas the *PSEN1* and *PSEN2* encode presenilin proteins which form the catalytic core of γ-secretase complex that is responsible for APP cleavage [14,15]. Specifically, pathogenic variants in these three genes are responsible for the development of FAD [14]. The effects of these variants are not uniform and can include changes in APP processing, *PSEN1* and the relative production of different Aβ species [15]. In addition to its role in APP processing, *PSEN1* has also been implicated in neurodevelopment through altered Notch signaling, showing that the effects of pathogenic *PSEN1* variants may extend beyond amyloid processing [16].

The APP protein is synthesized from the *APP* gene, subsequently it undergoes sequential proteolytic cleavage by β-secretase and γ-secretase, generating peptide fragments including amyloid-β (Aβ). Mutations in APP, such as the Swedish (KM670/671NL) and the London (V717I) mutations, lead to an increase in the overall amount of Aβ produced from *APP* and an increase in the generation of the aggregating Aβ42 isoform from *APP*, both of which accelerate the deposition of Aβ into plaques outside of the cell [14]. Pathogenic mutations in the APP gene are able to alter the γ-secretase-mediated processing, which leads to an increase in the production of aggregation-prone Aβ species which con-

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tribute to downstream neurodegenerative processes and atypical synaptic functionality. The cutting of *APP* to make the peptide fragments called amyloid-beta (Aβ) happens because of the *PSEN1* (*presenilin 1*) and *PSEN2* (*presenilin 2*) proteins, which are produced by the PSEN1 and *PSEN2* genes and are part of the γ-secretase complex that cuts *APP* at specific sites. More than 200 pathogenic variants have been reported in *PSEN1*, which accounts for a substantial proportion of autosomal-dominant early-onset AD cases [14,17]. The effects of *PSEN1* variants are not uniform; individual variants can alter γ-secretase-mediated APP processing and consequently influence the relative production of different Aβ species [14,15,17]. Therefore, the pathogenic effects of *PSEN1* variants should be considered in a variant-specific manner rather than being described solely as a uniform increase in the Aβ42:Aβ40 ratio.

Mutations of *PSEN2* are much less frequently reported; however, similar to *PSEN1* mutations, *PSEN2* mutations cause pathogenicity by dysregulating γ-secretase catalytic activity and producing an excess of Aβ. Pathophysiologically, mutations that occur in *PSEN2* are related to more variable clinical phenotypes in contrast to the mutations in PSEN1. However, both mutations can alter the γ-secretase activity, which results in an increased production of Aβ42 and contributes to the amyloid pathology [17]. Mutations in APP, *PSEN1*, and *PSEN2* have been important research tools for understanding how alterations in the amyloid pathway contribute to AD. Findings from these genetic studies have helped establish amyloid processing as an important therapeutic target and have contributed to the development of amyloid-targeting therapeutic strategies [18].

Table 1 Major Alzheimer's Associated genes, along with their biological roles, along with current/potential therapeutic strategies.

Gene	Role in AD	Biological role	Current/potential therapeutic strategy
APP	Familial AD	Aβ precursor; mutations alter Aβ production and aggregation	Amyloid-targeting therapies; experimental gene editing
PSEN1	Familial AD	γ-secretase component involved in APP processing	Experimental gene-targeted approaches
PSEN2	Familial AD	γ-secretase component involved in APP processing	Experimental gene-targeted approaches
APOE	Late-onset AD	Lipid transport and Aβ clearance	Pharmacogenomics; personalised medicine
TREM2	AD risk	Microglial activation and immune regulation	Potential immuno-modulatory therapies
SORL1	AD risk	APP trafficking and processing	Potential pathway-targeted therapies
BIN1	AD risk	Endocytosis and membrane trafficking	Potential pathway-targeted approaches
CLU	AD risk	Lipid metabolism and Aβ clearance	Potential therapeutic targeting

Risk Genes

The late-onset AD is highly complex in terms of its genetics and is also influenced by many susceptibility variants that have been identified by the Genome-Wide Association Study (GWAS) [1,2]. Different from familial AD, which is caused by penetrant mutations, Late Onset Alzheimer's Disease (LOAD) is caused by the cumulative effect of common genetic variants that modify the risk of the disease rather than directly determining disease onset [1,2].

The highly significant and consistently replicated genetic risk factor for LOAD is the apolipoprotein E (APOE) ε allele [1,19]. Moreover, individuals that are carrying one ε4 allele can demonstrate a substantially higher risk of developing AD, while homozygous ε4 carriers have a greater risk and earlier age onset compared to ε3 homozygotes [19]. In addition to increasing the vulnerability, the APOE ε4 allele is also linked to the increase in plaque deposition in the brain along with decreased Aβ clearance and increased amyloid-β aggregation [19]. The ε4 isoform worsens the synaptic dysfunction as well as the neuroinflammatory response by modifying the lipid metabolism and interfering with crucial repairs of neural pathways [19]. In contrast, the ε2 allele has a rather protective impact, which is due to the less inflammatory signaling and more effective Aβ clearance [1,19].

Detailed GWAS meta-analyses have identified numerous additional risk loci associated with the pathophysiology of AD [2,18]. These loci are overlapping on biological processes like endocytic trafficking, immunological modulation, and lipid transport [2]. Additionally, researchers mention *TREM2*, *CD33*, and *SORL1* widely in their research, which have a deep relationship with intracellular processing pathways and microglial activity [2,18]. The specific variants within *TREM2* impact inflammatory signaling along with amyloid plaque clearance by controlling microglial activation and phagocytic capabilities [2]. Similarly, the *SORL1* gene contributes to the intracellular trafficking of the *amyloid precursor protein* (APP), which impacts amyloidogenic processing, whereas the *CD33* gene influences the microglial responses [1,18].

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Genetic Risk Assessment in Alzheimer's Disease

Polygenic Risk Scores and Genetic Risk Stratification

Polygenic risk score (PRS) is a method utilized to measure the cumulative genetic vulnerability to a specific illness[20,21]. The GWAS identified many common variants, which the PRS aggregates. The PRS contains the risk factors for AD that go beyond APOE, such as specific variations that are found in detailed meta-analyses that link particular pathways to immunity, amyloid processing, and lipid metabolism[22]. The score is calculated as a weighted sum of genotype dosages using the equation

$$\text{PRS} = \sum \beta_i G_i \tag{1}$$

Where G_i is the allele dosage (0, 1, or 2 copies of the risk allele), and β_i is the log odds ratio obtained from GWAS summary data for variation i[20]. P-value criteria and linkage disequilibrium trimming or Bayesian shrinkage techniques to minimize redundancy are commonly used to decide variant inclusion[21].

The PRS values are then normalized within a reference population after the computation phase, which is most commonly through z-score transformation, which enables people to be categorized in highly specific genetic risk percentiles or deciles[21]. For that reason, instead of surpassing a fixed biological threshold, people with higher PRS are those who are present in the upper percentiles of the population distribution. For example, instead of the APOE genotype, a study by Kunkle et al. depicted that those in the highest decile of PRS had significantly higher odds ratios for AD in comparison to those present in the lowest decile[22]. Additionally, as per Escott-Price et al., people present in the top PRS quintile had the higher risk ratios for cognitive decline and the earlier onset of AD[23].

The odds ratios (OR), area under the receiver operating characteristic curve (AUC), and hazard ratios (HR) are widely used to investigate the predictive effectiveness of PRS in AD. Even though integration with APOE genotype is able to enhance discrimination around 0.70-0.75 in some groups of people, the PRS alone usually produces only modest discrimination (AUC $\approx$ 0.60-0.65)[20,21]. Importantly, increased PRS has been said to have a connection to increased tau pathology and amyloid-β deposition as shown by PET imaging and cerebrospinal fluid biomarkers that indicate a biological relationship with the disease's processes[24]. Additionally, longitudinal studies show that a higher PRS is predictive of a quicker clinical development and the transition from moderate cognitive impairment to Alzheimer's disease[23,24].

PRS is still population-dependent in spite of these developments. The majority of the GWAS datasets used to create AD PRS models are made up of people of European ancestry[21,22]. When European-derived PRS models are applied to non-European populations, cross-ancestry analyses show decreased prediction accuracy because of variations in allele frequencies and linkage disequilibrium structure[21]. As a result, PRS is still mostly only used in research settings in North America and Europe rather than becoming a standard clinical procedure worldwide.

Currently, the main applications of PRS include clinical trial enrichment, longitudinal modeling, and research stratification[21,22]. PRS enhances cohort selection and boosts statistical power in preventive studies by identifying those with higher cumulative genetic load[22]. However, PRS is utilized as a supplementary element within multi-modal predictive frameworks combining biomarkers and clinical factors rather than as a stand-alone diagnostic tool since its prediction accuracy at the individual level is still probabilistic and context-dependent[20,24].

Genetic Factors in AD Treatment

Pharmacogenomics

Due to numerous genetic variations that can influence therapeutic efficacy and its susceptibility to adverse drug responses, pharmacogenomics has started to receive more attention in AD research in order to understand inter-individual differences in treatment outcomes[25,26]. To create more individual specific treatment plans for dementia patients, pharmacogenomic research aims to ascertain how inherited genetic variations affect medication metabolism, treatment response and adverse-event risk[25,27]. The apolipoprotein E (APOE) genotype, specifically the $\varepsilon 4$ allele has been widely studied in AD pharmacogenetics, due to its established association with AD risk and also its potential role in modifying treatment response and adverse events related to treatment[26,27]. However, simply an association with disease risk should be distinguished from evidence that a genotype predicts treatment benefit.

The most often given medications for Alzheimer's disease symptoms are still cholinesterase inhibitors, such as galantamine, rivastigmine, and donepezil. By blocking acetylcholinesterase activity, these medications improve cholinergic neurotransmission in affected brain areas and increase the availability of acetylcholine in the synaptic clefts[26]. Despite numerous findings, substantial variation between individuals has been observed in response to cholinesterase inhibitors. Many pharmacogenomic studies have as a result investigated, if genetic variation can lead to differences in treatment response. For example, a study conducted by Weng et al. showed an association between CHRNA7 polymorphisms, which impact the $\alpha 7$ nicotinic acetylcholine receptor subunit, and response to the cholinesterase inhibitor treatment in patients with AD[28]. However, this shows an exploratory candidate-gene finding and thus requires independent replication before the CHRNA7 genotype can be deemed as clinically

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useful for guiding treatment decisions[28].

Evidence in relation to the influence of *APOE* genotype on response to cholinesterase inhibitors remains inconsistent. A pooled analysis of randomized clinical trials that evaluated donepezil, found no statistically significant *APOE*-by-treatment interaction based on ADAS-Cog scores, even though *APOE* ε4 carriers and non-carriers experienced cognitive improvement[29]. Similarly, Farlow et al. reported that response to rivastigmine treatment was predicted by the rate of disease progression[30]. Although, Choi et al. reported an association between *APOE* genotype and cognitive response to donepezil[31]. These findings must be considered different from evidence of a genotype-by-treatment interaction. Differences in study design, ethnicity, sample size, treatment duration and also outcome measures can contribute to discrepancies across studies, while numerous pharmacogenetic and clinical factors can also influence treatment outcomes[25,26,32]. Evidence containing *BCHE* polymorphisms in a similar manner remain exploratory and need independent replication and appropriate validation prior to it being considered as clinically actionable[31]. Overall, present evidence does not consider *APOE*, *CHRNA7* or *BCHE* genotype as reliable predictors of differential benefit from cholinesterase inhibitors.

The emergence of disease-modifying treatments for AD has made pharmacogenomics highly relevant. Monoclonal antibodies which target amyloid-β such as lecanemab and aducanumab, aim to reduce the amyloid pathology and slow the progression of the disease rather than stopping it entirely. The early clinical data showed the potential of antibody-mediated amyloid removal, with aducanumab reducing amyloid-β plaque burden in patients with AD[33]. However, the EMERGE and ENGAGE trials produced discordant clinical outcomes, with the EMERGE trial showing a significant reduction in clinical decline while ENGAGE did not meet its primary endpoint[27,33]. Biogen subsequently discontinued the development along with commercialization of aducanumab in 2024, which is why it should no longer be considered as a current treatment option[34,35].

Donanemab gives another disease-modifying treatment option for patients with mild cognitive impairment or rather mild dementia due to AD. Donanemab has also been investigated in the phase III TRAILBLAZER-ALZ 2 trial in patients with early symptomatic AD, with treatment was associated with differences in clinical decline according to baseline tau pathology. However, treatment was also associated with ARIA, particularly among APOE ε4 carriers[36]. In the low/medium-tau population, donanemab produced a 3.25-point smaller decline in iADRS compared with placebo[37]. Amyloid confirmation is also needed before treatment, and ARIA represents an important treatment-related safety concern[37]. The risk of ARIA-E and ARIA-H is much higher in APOE ε4 homozygotes than heterozygotes and non-carriers[37]. Similar to lecanemab, APOE genotype therefore appears to have a clearer role in predicting treatment-related safety than in determining therapeutic efficacy[37–39].

In contrast, the CLARITY-AD trial demonstrated that lecanemab slowed the functional and cognitive decline in patients with early AD over an 18-month period. Lecanemab produced a 0.45-point smaller increase in CDR-SB in comparison to placebo, which corresponds to an approximate 27% lesser clinical decline[34]. Amyloid confirmation is required before treatment, along with the MRI monitoring, which is necessary due to high risk of ARIA[34,39]. APOE ε4 carriers, specifically ε4 homozygotes, have a higher risk of ARIA, even though the current evidence does not establish a clinically meaningful difference in treatment efficacy according to APOE genotype[34,39].

Gene Therapy Approaches

Gene therapy shows an experimental therapeutic approach which aims to target genetic and molecular mechanisms implicated in AD. By changing genes or regulating their expression, these strategies seek to influence disease-related pathways instead of solely managing symptoms. However, the identification of a disease-associated gene or pathway does not solely establish itself as a validated therapeutic target. Current approaches involving gene editing, gene silencing and viral-vector delivery therefore remain primarily experimental and require more evidence of therapeutic efficacy and safety[40,41].

CRISPR/Cas9 editing of APOE or APP

CRISPR/Cas9 gene editing is a genome modification approach that allows the accurate changing of DNA sequences that are associated with AD[40]. The Cas9 endonuclease is guided by the RNA to a specific genome locus, thereafter it induces a double-stranded break. This break is then repaired by specific cellular processes that allow the correction or disruption of target genes[40,42]. In AD research, this approach has been investigated as a potential strategy for targeting genes such as *APP* and *APOE*[40]. Editing APP has been investigated as a possible method of reducing amyloid-β production and the subsequent formation of plaque, while modification of the *APOE* ε4 allele has been proposed as a strategy to reduce its pathogenic effects[40,42]. These findings provide a mechanistic rationale for gene-based intervention but fail to establish either of the approaches as a clinically validated one. Adding to that, these approaches show how CRISPR-based interventions could potentially target upstream disease mechanisms rather than downstream symptoms. However, in spite of this precise method, the approach faces certain challenges. The first of these are off-target mutations, which may introduce certain unintended genetic alterations, and permanent genome modification also raises many ethical and safety concerns[42]. More-

Table 2 Comparison of anti-amyloid therapies in Alzheimer's disease and the role of APOE genotype in treatment efficacy and safety

Feature	Lecanemab	Aducanumab	Donanemab
Regulatory status	FDA approved for early AD	Development and commercialization discontinued in 2024	FDA approved for early AD
Disease stage treated	MCI or mild dementia due to AD	MCI or mild dementia due to AD	MCI or mild dementia due to AD
Amyloid confirmation before treatment	Required	Required	Required
Primary endpoint	CDR-SB	CDR-SB	iADRS
Trial duration	18 months	78 weeks	76 weeks
Absolute treatment effect	0.45-point smaller increase in CDR-SB; approximately 27% less decline	EMERGE showed a clinical benefit, whereas ENGAGE did not meet its primary endpoint	3.25-point smaller decline in iADRS in the low/medium-tau population
ARIA-E	12.6%	35%	24.4%
ARIA-H	17.3%	28%	31.3%
APOE $\varepsilon 4$ effect on safety	ARIA risk substantially higher, particularly in $\varepsilon 4$ homozygotes	ARIA risk higher in $\varepsilon 4$ carriers, particularly homozygotes	ARIA-E and ARIA-H substantially higher in $\varepsilon 4$ homozygotes
Effect of genotype on efficacy	No clinically established differential efficacy	No clinically established differential efficacy	No clinically established differential efficacy
MRI monitoring	Required before and during treatment	Required before and during treatment	Required before and during treatment
Clinical role of APOE genotype	Primarily informs ARIA risk	Primarily informs ARIA risk	Primarily informs ARIA risk

over, the efficiency of in vivo editing within neuronal tissue also remains limited, which is specifically due to delivery constraints and cellular repair[42]. Consequently, researchers have confined CRISPR-based therapies for AD to preclinical and experimental stages of development[40,42].

RNA interference for mutant gene silencing

Another technique is RNA interference, which represents a post-transcriptional gene regulation approach that is designed to suppress the expression of specific genes that are associated with diseases without altering the DNA sequence[42]. This mechanism has small interfering RNA (siRNA) or short hairpin RNA (shRNA), which each, respectively, bind to a complementary messenger RNA (mRNA) molecule, leading to their degradation along with the prevention of translation into functional proteins[42]. In AD, RNAi has been investigated to reduce the expression of key pathological genes, for example, APP, *BACE1* (β-secretase), and other tau-related genes[42]. By reducing the expression of genes in relation to amyloid-β and tau pathways, RNAi gives a mechanistic approach for targeting processing implicated in neurodegeneration[42]. Unlike CRISPR, RNAi has a more controlled and reversible method of gene modulation that reduces the specific risks that are associated with permanent gene changes[42]. Despite its therapeutic potential, evidence for consistent clinical benefit remains limited. This limitation is due to the fact that gene silencing is a technique that is often transient, meaning that it needs repeated administration. The efficient delivery to specific neuronal populations remains a significant challenge in RNAi-based therapies[42]. Furthermore, changes in gene knockdown efficiency in many different cell types can overall reduce the consistency of the treatment[42].

Viral vector delivery challenges

One of the major obstacles in translating gene therapy approaches for AD into clinical treatment is the effective delivery of genetic material to the central nervous system[26,43]. This process is made possible with the implementation of viral vectors, which primarily include adeno-associated viruses (AAVs), that are used widely due to their ability to transport genetic material to host cells, which enables the long-term expression of therapeutic genes[42,43]. AAV vectors work by transporting engineered DNA sequences into specific target cells, wherein they are responsible for driving protein expression while still being episomal[42]. These vectors can be modified to benefit neuronal specificity, which also makes them the most appropriate for targeting brain tissue[43]. Despite this, AAVs are limited by some biological factors such as the blood-brain barrier, which inhibits systemic delivery and often necessitates invasive methods like intracranial injection[43]. Moreover, the immune response to these viral vectors can lower the treatment efficacy and can also lead to adverse effects[42,43]. AAV vectors have a limited packaging capacity which is another disadvantage, since it restricts the size of transgenes that can be delivered, which limits the design and complexity of therapeutic constructs[43].

Personalized Medicine and Stratified Trials

The role of personalized medicine in AD involves personalizing therapeutic approaches according to an individual's genetic, biomarker along with clinical profile. Instead of applying uniform treatment strategies, this approach aims to account for inter-individual differences in disease mechanisms

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and treatment response[25,27]. However, genetic information should only be used to guide treatment decisions in cases where evidence shows that a marker has predictive value for treatment efficacy or safety. A central component of this approach is therefore the integration of genetic information into clinical trial design and therapeutic decision-making while separating established predictive markers from genetic factors which remain investigational[20,24].

Genotype-Guided Trial Designs

Genotype-guided trial design is a method that stratifies participants on the basis of their genetic and biomarker-defined risk, which allows therapies to be tested in biologically relevant subgroups[20–22]. On a mechanical level, these types of trials involve the grouping of individuals on the basis of variants such as *APOE* genotype of polygenic risk scores, which influence amyloid deposition and disease progression[20,21,24].

The A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer's) study provides an example of biomarker enrichment instead of genotype-guided trial design. The study had cognitively normal individuals with higher amyloid burden identified through PET imaging, as a result it enriches the study population with individuals at higher risk of disease progression[24,44]. In contrast, the DIAN-TU (Dominantly Inherited Alzheimer Network Trials Unit) trials show a genetically defined trial design, since they enrolled individuals from families carrying an autosomal-dominant mutations in APP, *PSEN1* or *PSEN2*, which enables the investigation of therapies in a population with a genetically established risk of developing AD[14,45].

An alternative approach is prespecified genotype subgroup analysis, wherein treatment outcomes are analyzed separately as per the genetic status without restricting enrolment exclusively to individuals carrying a specific variant. This approach can aid in determining whether genetic differences modify treatment response while maintaining wider participant eligibility.

In therapeutic trials involving monoclonal antibodies such as lecanemab, participants may also be stratified according to *APOE* $\varepsilon 4$ status because of its association with amyloid pathology, disease progression, and treatment-related adverse events such as amyloid-related imaging abnormalities (ARIA)[25,27,34]. Importantly, this stratification does not by itself establish APOE genotype as a predictor of treatment efficacy. Rather, current evidence provides a clearer basis for considering APOE genotype in the assessment of treatment-related safety, particularly ARIA risk[25,27]. Necessary biomarker confirmation prior to treatment demonstrates another distinct form of enrichment and should not be considered inherently genotype guided. For example, requiring confirmation of amyloid pathology prior to administration of an anti-amyloid therapy selects participants as per their biological disease status instead of genetic status.

However, genotype-guided designs also have important limitations. Restricting a trial to a genetically defined population can reduce the generalizability of findings to the broader AD population, particularly across diverse ancestries[21,22]. Furthermore, a genetic marker that predicts disease risk or progression does not necessarily predict treatment benefit. Genetic, environmental, and lifestyle factors may interact to influence treatment outcomes, meaning that evidence of a genotype-by-treatment interaction is required before a genetic marker can be considered a reliable predictor of therapeutic response[20,24].

Companion Diagnostics

Companion diagnostics are a precision medicine approach that integrates biomarker and genetic information to support treatment selection and risk stratification[24,25]. However, the clinical value of each component depends on the evidence supporting its predictive role. Biomarkers or genetic markers associated with disease status or treatment-related risk should therefore be distinguished from validated predictors of treatment efficacy[25,27].

In AD, companion diagnostics combine genetic information such as APOE genotype with biomarker assessments including amyloid PET imaging and levels of tau and amyloid-β proteins in cerebrospinal fluid. These assessments can be used to establish the presence of disease-related pathology or to identify treatment-related risks, but they should not be considered predictors of treatment efficacy unless a validated genotype-by-treatment effect has been demonstrated[24,44,46].

For example, amyloid PET imaging is a widely implemented biomarker assessment and also an inclusion criterion in clinical trials like A4, which ensures that only biomarker-positive individuals are enrolled[24,44]. This represents biomarker-based enrichment rather than genetic prediction of treatment response. Additionally, *APOE* $\varepsilon 4$ genotyping is relevant to treatment decisions involving monoclonal antibody therapies because $\varepsilon 4$ carriers have a higher susceptibility to treatment-related adverse effects such as ARIA[25,27,34]. Evidence from trials like the CLARITY-AD trial supports this genotype dependent difference in the safety outcomes[34]. However, the use of APOE genotype to assess ARIA risk should be distinguished from using the genotype to predict differential therapeutic efficacy.

In spite of these advances in companion diagnostics, the actual implementation of these diagnostics in a consistent manner is quite limited. This is due to higher costs, which cause restricted accessibility of imaging machinery and variability in biomarker thresholds, which presents significant barriers[24,46]. In addition, ethical concerns related to genetic testing, particu-

larly in asymptomatic individuals, complicate the widespread adoption and raise concerns about the psychological impact and clinical utility of these diagnostics[25,27].

Table 3 Evidence linking genetic factors to Alzheimer's disease treatment response and safety

Treatment	Genetic factor	What it predicts	Evidence level	Clinical relevance
Cholinesterase inhibitors	*APOE*	Differential treatment benefit	**Not validated**	No significant *APOE*-by-treatment interaction demonstrated[29]
Cholinesterase inhibitors	*CHRNA7*	Treatment response	**Exploratory association**	Requires independent replication[28]
Cholinesterase inhibitors	*BCHE*	Treatment response	**Exploratory association**	Not yet clinically actionable[32]
Anti-amyloid antibodies	*APOE* ε4	ARIA risk	**Replicated association**	Relevant to treatment safety[25,27,38]
Anti-amyloid antibodies	*APOE* ε4	Differential treatment efficacy	**Not established**	Genotype should not currently be interpreted as a predictor of treatment benefit[38]
CRISPR-based approaches	*APP, APOE*	Potential modification of disease mechanisms	**Mechanistic hypothesis**	Preclinical /experimental; not a validated treatment[40,41]
RNA interference	APP, BACE1, tau-related genes	Potential reduction of pathological processes	**Mechanistic hypothesis**	Experimental approach; clinical benefit not established[42]

The current evidence linking genetic factors to AD treatment can be summarized according to whether the genetic factor predicts treatment response, treatment-related safety, or only provides a mechanistic basis for therapeutic development (Table 3).

Challenges and Limitations

Genetic Heterogeneity and Epistasis

Genetic heterogeneity and epistasis are key biological challenges that limit the usage of genetically informed approaches in the treatment of AD. Instead of being driven by a single causal mutation, LOAD generally arises from a combination of effects of numerous genetic variants, most of which have modest individual effects, although major risk factors such as the *APOE* ε4 allele can increase disease risk to a great extent[1,2,20]. Due to the complexity of the genetics, the predictability of individual biomarkers is reduced, along with complicating the development of personalized therapeutic strategies.

Genetic Heterogeneity

The term "genetic heterogeneity" refers to the existence of many unique genetic variants, which all contribute to the phenotype of a particular disease, largely through different biological pathways. In the context of AD, the term has variants involved in aspects like lipid metabolism, immune regulation, amyloid processing, and endocytic trafficking[2,18,22]. The GWAS has found multiple susceptibility loci, like *APOE*, *TREM2*, *CD33*, and *SORL1*; each of these contributes to overall disease risk[2,18,22]. These genes influence processes such as amyloid-β clearance, intracellular protein trafficking, and microglial activation that led to multiple parallel pathways that contribute to neurodegeneration[2,18]. Because of this variation, individuals with comparable clinical symptoms may possess different underlying biological processes.

As a result of this variability, therapeutic approaches now target a single pathway, such as amyloid-β reduction, which might not have the same impact for all groups of patients. For example, while amyloid-targeting monoclonal antibodies show plaque reduction, inconsistencies are still present in terms of their clinical benefits, which shows their genetic and biological heterogeneity among various patients[8,34]. This study is also able to highlight a crucial limitation, which is that heterogenous disease mechanisms can significantly reduce the generalizability of the findings along with the efficacy of uniform treatment strategies.

Epistasis (Gene-Gene interactions)

Epistasis talks about the interaction between genetic variants when one gene's effect is being modified by the presence of another gene. These interactions can contribute to disease risk and progression; however, they are not captured by a single-variant analysis like the GWAS or polygenic risk score in relation to AD[20,21].

These epistatic interactions could occur between a set of genes that are all involved in related biological pathways. For example, interactions between other genes that regulate immune response or lipid metabolism and *APOE* can amplify or mitigate disease risk beyond the prediction of each gene on an individual level[20,24]. Also, this study is able to show that AD risk is not just additive but instead has non-linear and complex genetic relationships. On the other hand, despite their significance, these effects remain challenging to quantify and identify. This is due to the presence of many statistical and methodological challenges.

Moreover, the majority of the large-scale genetic studies are designed in a manner in which they are able to detect the effects of the independent variable instead of a set of interactions, which leads to the underrepresentation of epistasis in present models of AD's genetics[21]. Due to this, even predictive tools like the PRS can fail to fully capture the complexity

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Table 4 Summary of reviewed studies examining genetic factors and Alzheimer's disease treatment

Author/year	Study design	Sample characteristics	Genetic marker(s) examined	Primary treatment-related findings	Stated limitations
Weng et al., 2013 [28]	Candidate-gene association study	204 patients with mild–moderate AD receiving cholinesterase inhibitors; recruited from 3 teaching hospitals in Taiwan	**CHRNA7** polymorphisms	CHRNA7 variants, particularly rs8024987, were associated with better cognitive response to cholinesterase inhibitors; association was strongest among women and galantamine users. (PubMed)	Exploratory finding requiring independent replication before clinical implementation
Waring et al., 2015 [29]	Pooled analysis of randomized clinical trials	Patients with mild–moderate AD from 3 multinational, 12-week randomized studies of donepezil and placebo	**APOE ε4**	No significant APOE-by-treatment interaction was detected; both ε4 carriers and non-carriers receiving donepezil showed cognitive improvement. (PubMed Central (PMC))	Pooled analysis; findings apply to the studied trial populations and do not establish APOE as a predictive treatment biomarker
Farlow et al., 2001 [30]	Randomized placebo-controlled trial followed by open-label extension; retrospective analysis	187 patients with mild–moderately severe AD who received placebo for 26 weeks followed by rivastigmine for 26 weeks	**No treatment-genetic marker was directly examined**	Rate of disease progression before treatment predicted subsequent response to rivastigmine; this study does not directly establish an APOE-dependent treatment effect. (PubMed)	Retrospective analysis; genetic factors such as APOE were discussed as possible influences on progression but were not the treatment-response marker tested in the study
Choi et al., 2008 [31]	Open-label clinical treatment-response study	51 patients with probable mild–moderate AD treated with donepezil for 48 weeks; 18 were APOE ε4 carriers	**APOE ε4**	APOE ε4 carriers showed a different cognitive response to donepezil than non-carriers, with the authors reporting a possible association between ε4 status and treatment response. (PubMed)	Small sample and open-label design; findings do not establish a genotype-by-treatment interaction
Sevigny et al., 2016 [33]	Randomized, placebo-controlled clinical trial/biomarker study	Patients with AD receiving aducanumab; amyloid plaque burden assessed longitudinally	**APOE** considered in relation to treatment effects/safety	Aducanumab produced dose- and time-dependent reductions in amyloid plaque burden. (PubMed)	Amyloid reduction does not by itself establish a clinically meaningful genotype-dependent treatment benefit
Haeberlein et al., 2022 [38]	Two randomized, double-blind, placebo-controlled phase III trials (EMERGE and ENGAGE)	1,638 participants in EMERGE and 1,647 in ENGAGE; early AD; confirmed amyloid pathology; 20 countries	**APOE** examined among treatment-related factors	EMERGE met its primary endpoint, whereas ENGAGE did not; both studies demonstrated amyloid/pathophysiological target engagement. (PubMed)	Discordant outcomes between the two phase III trials limit interpretation of the overall clinical efficacy
van Dyck et al., 2022 [34]	Randomized, double-blind, placebo-controlled phase III trial (CLARITY-AD)	1,795 participants with early AD; MCI due to AD or mild AD dementia	**APOE ε4**	Lecanemab slowed clinical and functional decline over 18 months; APOE ε4 status was particularly relevant to ARIA risk, with higher risk among ε4 carriers and especially homozygotes. (PubMed)	Differential treatment efficacy according to APOE genotype was not established
Zimmer et al., 2025 [36]	Secondary safety analysis of randomized clinical trials	984 donanemab-treated and 999 placebo-treated participants from pooled placebo-controlled portions of TRAILBLAZER-ALZ and ALZ 2, plus 1,047 donanemab-treated participants in an open-label addendum	**APOE ε4**	ARIA-E and ARIA-H were substantially more frequent among APOE ε4 carriers, with the highest rates among ε4 homozygotes. (JAMA Network)	Primarily evaluates treatment-related safety/ARIA, rather than establishing APOE genotype as a predictor of therapeutic efficacy

of genetic risk in AD, which limits their clinical usefulness as well as accuracy [20,24].

Ethical Considerations

In AD research and treatment, the usage of genetic information introduces a huge ethical challenge, which relates to genetic testing, equitable access to new therapeutic strategies, and the usage of data. This is despite the fact that these genetic approaches provide opportunities for personalized treatment and early diagnosis; they pose concerns about the psychological impact, privacy, and inequalities in the access to healthcare.

Thereafter, the usage of genetic testing in AD creates important ethical concerns in relation to its predictive nature and clinical usefulness. Genetic tests like the *APOE* genotyping and PRS give rough estimates of the disease risk rather than a concrete diagnosis; this is especially visible in LOAD, where multiple genetic and environmental factors lead to the onset of AD [20,21,24]. Because of these factors, individuals that have been identified as high-risk may be susceptible to psychological distress and manipulated life decisions even though there is an absence of effective preventive measures [25]. This study brings attention to an important limitation of current approaches, which includes the provision of risk information in the absence of related therapeutic action that can possibly lead to harm rather than a true clinical benefit. Additionally, even a simple misinterpretation of results can increase the need for appropriate genetic counseling [20,25].

Moreover, the growing usage of genetic data in AD treatment also creates an argument about the privacy and potential misuse of information, which is extremely confidential and personal to the patient. These genetic data are inherently identifiable and are stored in large scale data bases, which in-

creases the potential risk of data breaches and unauthorized access to data[25]. Consequently, this issue also increases the potential for genetic discrimination in areas like employment and insurance, wherein the scope of regulatory protections differs considerably across different places, with some authorities providing more comprehensive safeguards than others[25].

Another significant challenge in the approach of genetic approaches in AD treatment is equity. Most of the already existing genetic research that primarily includes the GWAS and PRS models is based majorly on populations that have a European ancestry, which reduces the generalizability of the findings and also the predictive accuracy and reliability of these largely used tools in other more diverse populations[21,22]. The differences in specific allele frequencies can lead to certain inaccurate judgements in the context of risk estimation when these research findings are applied more broadly to wider populations[21]. Adding to that, access to genetic testing and biomarker-based therapeutic strategies remains to be exclusive due to extremely high costs and lack of healthcare infrastructure in underprivileged communities, which creates inequalities in both research participation and clinical benefits.

Translation from Bench to Bedside

Both genetic and molecular advancements in AD research face challenges in being translated into appropriate and effective therapeutic strategies. Even though genomic studies have helped identify disease associated pathways and genes, translating these findings into targeted therapies remains limited by challenges in experimental validation, clinical trial design along with biomarker development[1,18]. A major restriction is the limited translational validity of preclinical models. Numerous experimental systems, which include the transgenic animal models, are designed to reproduce certain pathological features such as amyloid-β accumulation but many fail to fully capture the multifactorial and progressive nature of AD. Consequently, therapeutic strategies focused on genetically informed mechanisms may show promising results in controlled experimental settings but fail to achieve comparable efficacy in clinical trials, this shows the gap between the human disease process and experimental findings[15,18].

A further challenge is determining whether genetically identified associations can represent actionable therapeutic targets. The presence of a disease-associated variant does not necessarily indicate that modifying the corresponding gene or pathway will reverse the pathology established. Genetic variants may influence AD through complex biological networks, and the same gene can have different impacts dependent on the stage of the disease, cellular context or interactions with other genetic factors[24]. As a result, identifying a genetic association is only an initial step and functional validation is imperative to establish whether modifying the associated pathway can produce a meaningful therapeutic effect.

The translation of genetically informed findings into significant clinical trials also presents important challenges. Genetic targets may influence AD over long periods before clinical symptoms are evident, this makes it difficult to determine the appropriate stage at which an intervention should be introduced. Furthermore, genetic differences between patients can lead to variation in disease progression and treatment response, which complicates the identification of meaningful therapeutic. Clinical trials must thus account for genetic and biological heterogeneity when evaluating if targeting a specific pathway produces a consistent clinical benefit[24,25].

Therapeutic implementation also remains challenging for interventions which are directly targeting genetic mechanisms. Gene based therapies thus require precise and sustained modification of the intended target, while effective delivery to the central nervous system remains a major consideration. Moreover, translating genetically targeted approaches from experimental models into treatments suitable for diverse patient populations which need further validation of their safety, efficacy along with long-term effects[25].

Future Directions

Multi-Omics Integration

The multi-omics integration demonstrates a more system-level method which integrates factors like genomics, epigenomics, transcriptomics and proteomics, which gives a more detailed understanding of AD[2,18,47,48]. Although numerous genetic studies have identified many risk loci, they often are unable to capture how these specific variants can lead to changes in downstream biological processes. The multi-omics approach addresses this disadvantage by linking genetic variation to functional outcomes like protein activity and gene expression[47,48]. This process is completed through the integration of datasets throughout many biological layers. For example, cumulating the GWAS data with proteomic and transcriptomic profiles to identify pathways that are dysregulated and have a connection with the progression of the disease[2,18,47]. This helps clinicians in the identification of key regulatory networks instead of isolated genes, which gives a more holistic view of the pathophysiology of AD[47,48]. These approaches are being used more commonly to help identify specific biomarkers and therapeutic targets that reflect the complexity of AD[48].

However, many challenges still exist especially in terms of standardization, interpretation and data integration. Also, since the multi-omics datasets are large, they require advanced computational tools for a meaningful analysis to take place[47]. Moreover, the variability in these datasets and populations limit the reproducibility and clinical translation of therapeu-

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tics[48]. In spite of these problems, the integration of the multi-omics approach has a strong potential to enhance the disease modeling and precision medicine approaches in AD treatment.

AI-Driven Genetic Modelling for Drug Discovery

AI and machine learning are emerging computational approaches for speeding up drug discovery and helping in analyzing complex genetic data in the context of AD[47,49]. The traditional approaches are limited by the sheer scale and complexity of these genomic datasets, whereas new AI-driven models are able to integrate multi-dimensional data to identify predictive relationships and patterns[49]. AI algorithms can also combine biomarker, genetic, and clinical datasets to model the progression of the disease and emphasize specific therapeutic targets. For example, machine learning models can identify specific gene networks that are associated with disease risk and can even simulate drug-target interaction while also predicting treatment responses in silico[47,49]. This approach has the potential to reduce both the cost and time that are associated with the early stages of drug development.

Nonetheless, the utility of AI models is dependent on the quality and diversity of the data being inputted. Many biases in genetic datasets, which include the underrepresentation of non-European populations, can significantly limit the generalizability of the AI models' findings[21,49]. Adding to that, the restricted interpretability of certain AI models presents many challenges in terms of clinical validation and regulatory approval[49].

Longitudinal Studies on Gene-Environment Interactions

Longitudinal studies that investigate interactions between genes and environment have a dynamic approach that aims to understand how genetic predisposition can interact with one's lifestyle and environment over a period of time[20,24,50,51]. Even though genetic risk factors like *APOE* ε4 contribute to AD susceptibility, they do not act in isolation, and their effects can possibly be manipulated by a set of behavioral and environmental factors[20,24,52]**?** . Longitudinal cohort studies can track a specific set of individuals over extended time periods, which integrates genetic data with environmental variables and clinical outcomes. This allows the researchers to identify temporal patterns of disease progression and also helps them in assessing how certain environmental factors could potentially influence the expression of genetic risk[50,51]. These approaches are specifically valuable to identify modifiable risk factors and inform certain preventive strategies.

However, these longitudinal studies require plenty of resources as well as a large, well-characterized cohort with long follow-up periods. Other challenges like participant attrition, confounding variables, and differences in data collection can lead to a reduction in the reliability and validity of the study[50]. Additionally, isolating the effects of specific interactions between genes and environment remains methodologically complex[52].

Conclusion

Alzheimer's disease is a very complex neurodegenerative disease that has many genetic factors affecting susceptibility and drug response. This review highlights the tight association of pathogenic mutations of APP, *PSEN1* and *PSEN2* to familial Alzheimer's disease and the polygenetic nature of late-onset Alzheimer's disease (LOAD) which can be partially attributed to common genetic polymorphisms such as *APOE* and other risk loci identified through GWAS.

In this review, these genetic factors have been emphasized as playing a crucial role in the pathogenesis of the disease and in the variability of the disease and the response to treatment. Although the field of therapeutic variability has been enriched by the advent of pharmacogenomics and personalized medicine, there are challenges in the predictiveness, implementation and translational application of these areas. Adding to that, new approaches such as gene therapy and genotype-specific clinical trials contain significant potential for clinical application. However, further validation of their long-term benefits, efficacy and also safety is required prior to widespread adoption in clinical practice.

Overall, these findings emphasize the need for a multimodal treatment approach for Alzheimer's disease, a multifactorial disease. Future advances in the field might be possible by integrating molecular, genetic and environmental data, using multi-omics approaches, constructing AI-supported models, or by following gene–environment interactions over time, etc. These advances may help to predict disease, identify new therapeutic targets, and lead to the creation of more accurate, effective and available treatments for Alzheimer's disease.

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