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Epigenetic Mechanisms and Gene Therapy in Late-Onset Alzheimer's Disease: Molecular Pathogenesis, Therapeutic Targets, and Translational Challenges

Marwan Jaber[1], Nourelhuda Mohamed[1], Ayesha Inam[2], Samria Suganth[3], Mayank Dadhich[4]

[1]Depertment of Medicine, School of Health Sciences, University of Georgia, Tbilisi, Georgia; [2]Faculty of Medicine, Central University Of Europe (CUE), Kutaisi, Georgia; [3]Department of General Medicine, Yerevan State Medical University, Yerevan, Armenia; [4]Faculty of Medicine, Georgian American University, Tbilisi, Georgia

ORCID: Marwan Jaber: 0009-0008-9658-61361, Nourelhuda Mohamed: 0009-0007-1479-09702, Ayesha Inam: 0009-0006-9736-31913, Samria Suganth: 0009-0005-0331-71714, Mayank Dadhich: 0009-0006-1788-4094

Corresponding author: Marwan Jaber, marwanmjaber@gmail.com, +995595127118.

Abstract

Late-onset Alzheimer's Disease (LOAD) represents a growing global health crisis, characterized by a complex interplay between genetic predisposition and environmental influences. While traditional therapeutic efforts have largely targeted amyloid-β and tau proteopathy with limited clinical success, attention has shifted toward the "epigenetic landscape" as a primary driver of neurodegeneration. This review explores the multifaceted roles of epigenetic mechanisms—including DNA methylation, histone modifications (acetylation and methylation), and non-coding RNA (miRNA, lncRNA, and circRNA) regulation—in the molecular pathogenesis of LOAD. We synthesize recent evidence demonstrating how dysregulation of these mechanisms leads to synaptic dysfunction, neuroinflammation, and impaired cognitive resilience. Furthermore, this review evaluates the emerging frontier of gene therapy and epigenome editing as transformative therapeutic strategies. We discuss the application of Adeno-Associated Virus (AAV) and lentiviral vectors in delivering neurotrophic factors and the potential of CRISPR/Cas9-based systems for precise modulation of risk genes like APOE4 and BACE1. Despite the promise of these biotechnological advances, significant translational challenges remain, including blood-brain barrier permeability, off-target effects, and the necessity for long-term safety profiles in an aging population. By integrating current knowledge of epigenetic shifts with the latest innovations in gene delivery, this review outlines a roadmap for precision medicine in Alzheimer's therapy, emphasizing the transition from broad-spectrum interventions to targeted molecular modulation.

Keywords: Alzheimer's disease, gene therapy, epigenetics, tau proteins, amyloid-beta

Introduction

Alzheimer is a neuro oriented disorder which effects the brain it basically suppresses the function of the brain and it is emerging as the common disease in this developing world as it is effecting the people's of older age more there is a gradual decline in memory and cognitive functions , however aging remains the prominent factors of this disease but there are several more factors associated to it. The classical neuropathological hallmarks of AD include the extracellular accumulation of amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein which shows neuronal loss and dysfunction, growing evidences also show that this disease extend beyond this frame including additional mechanisms such as mitochondrial dysfunction, oxidative stress, lipid dysregulation and cerebrovascular impairment, Emerging research show that if cerebral vasomotor is effected then there will be reduced blood flow and diminished clearance of Aβ, whereas synaptic and molecular alterations may occur independently of amyloid and tau pathology (1, 2). Genetic factors play a crucial role in AD pathogenesis linked to mutation in APP, PSEN1 and PSEN2, there can be multiple susceptible genes like apolipoprotein E linked to late onset Alzheimer , genes influence and interact with key biological pathways including lipid metabolism, immune regulation and synaptic function. Sex specific differences affect variability in genomic regulatory architecture affecting heterogeneity of AD genetic risk factors not only increase susceptibility but also influence the trajectory of cognitive decline over time. Epicene tic regulation is a critical layer in Alzheimer disease, dysregulated gene activity is done by alteration in DNA methylation, his tone modification and non-coding RNA expression Notably, epigenetic and transcriptomic changes may precede amyloid deposition, suggesting that early molecular disturbances occur well before clinical manifestation, the reversible nature of epicene tic modifications presents promising opportunities for therapeutic intervention (3). Diagnosis and staging of AD has been improved by bio marker research and neuroimaging, techniques used are amyloid and tau positron emission tomography which enables in vivo visualisation of pathological changes, detecting early changes. Large-scale initiatives, including the Alzheimer's Disease Neuroimaging Initiative (ADNI) and international collaborations such as CONCORD-AD, have played a pivotal role in standardizing data collection, validating biomarkers, and enhancing the generalizability of research findings across diverse populations these all methods have problem in cost, accessibility and translation of bio markers (4).

Methodology

This narrative review of epigenetics and gene therapy in late-onset Alzheimer's disease (LOAD) includes different types of studies such as original research articles, observational studies, epigenome-wide association studies, preclinical gene therapy studies, and review studies.

A search was conducted across multiple electronic databases, including PubMed, Scopus, and Cochrane Library. The search combined keywords related to Alzheimer's disease, such as ("Alzheimer's disease",

"late-onset Alzheimer's disease", "LOAD"), with "epigenetics" and "gene therapy". Boolean operators (AND, OR) were used to refine the search and ensure that all relevant studies were included.
Inclusion criteria were to review observational studies, or epigenome-wide association studies focusing on humans with late-onset Alzheimer's disease or relevant animal models. Studies had to be published in English and include any type of epigenetic mechanism or gene therapy.
Exclusion criteria were case reports, opinion pieces, conference abstracts without full text, and studies focusing on other types of therapies. Studies focusing on other than Alzheimer's pathways or early onset of AD, those with no epigenetic or gene therapy focus, other types of dementia, and articles not published in English.
After induplication, title/abstract screening, and text-full text screening, 72 articles met the inclusion criteria and were selected for analysis.

Results

DNA methylation refers to formation of 5-methylcytosine (5mC) by a covalent bond with the cytosine 5′ carbon site of the CpG dinucleotide in the genome under the action of DNA methyltransferases (DNMTs). In addition to 5mC, hydroxymethylation at the 5-position of the cytosine base (5hmC) derived from the oxidation of methylated cytosines by ten-eleven translocation (TET) enzymes is another epigenetic regulatory mechanism, which is particularly abundant in the brain (5). 5-methylcytosine (5mC) functions as a transcriptional repressor by either physically obstructing the binding of transcription factors to promoter regions or by recruiting methyl-CpG-binding proteins. These proteins facilitate chromatin remodeling into a condensed, inactive state, effectively silencing gene expression. 5hmC is the intermediate product of DNA methylation and demethylation,which adds a layer of complexity to the epigenetic regulation of both verified in AD patients 5mC and 5hmC levels were significantly lower in the hippocampus than those of negative controls. Neurofibrillary tangle deposition in the same hippocampus cells was inversely proportional with 5mC levels (6, 7).
According to two investigations, there is no discernible difference between AD patients and normal controls in terms of DNA methylation levels in postmortem brain tissues. But when Foraker et al. examine the methylation profiles of AD postmortem brains in vitro, they find a notable drop in APOE DNA methylation levels. The detecting platform could be the cause of this discrepancy (8, 9). The APOE promoter regions devoid of CpG islands based on bead-chip are the primary focus of the preceding two investigations. Pyrosequencing, which is more accurate in representing APOE methylation levels, is used in the next investigation to acquire CpG methylation of APOE . Another study shows that the low levels of APOE DNA methylation in AD patients are primarily caused by non-neuronal cells (10).

Histone modification

Histone is a kind of octamer consisting of pairs of H2A, H2B, H3, and H4, which form the nucleosome with DNA. Histone can be modified at the N-terminal tails, and the modifications can affect the three-dimensional structure of the chromatin, leading to the changes in the transcription of genes (11). The main types of histone modifications include acetylation, methylation, phosphorylation, ubiquitination,

and ADP glycosylation (3, 12). Methylation is usually associated with gene silencing and acetylation is associated with gene activation (13).

Histone methylation

Histone methylation refers to the addition of methyl groups to specific amino acid residues of histones. Lysine can be monomethylated, dimethylated, or trimethylated, whereas arginine can be monomethylated or dimethylated. Histone methylation is catalysed by the histone methyltransferase (HMT) enzyme, which can add the methyl group of the S-adenosylmethionine donor to its target residue (14). In the brains of AD patients, some histone methylation markers (like H3K9me2 and H3K4me3) are markedly elevated or lowered. These markers are linked to pathological Aβ accumulation, tau protein hyperphosphorylation, neuroinflammation, synaptic dysfunction, and memory and cognitive impairment (15, 16). The decrease in the expression levels of the glutamate receptor subunits AMPAR and NMDAR, which are essential for the proper operation of neurons, are linked to an increase in H3K9me2 levels. An increase in H3K9me2 is also linked to the downregulation of glutamate receptor expression,While alterations in H3K4me3 are linked to immune response pathway activation and synaptic function damage (2, 17).

Histone acetylation

Histone acetylation is the addition of acetyl groups to the ε-amino group of histone lysine residues under the catalytic action of histone acetyltransferase (HAT), neutralizing the positive charge of lysine and changing the charge state of histones. Histone deacetylase (HDAC), on the other hand, is in charge of eliminating acetyl groups from lysine residues (18, 64). Through altering chromatin openness, quick histone marker turnover, and dynamic DNA factor recruitment, histone acetylation may control gene expression and impact transcription processes (19).

Non coding RNAs

Non-coding RNAs (ncRNAs) are defined as RNA molecules that are not translated into a protein [5]. Although they do not directly participate in protein synthesis, they play multiple important biological functions in cells (20, 63). Noncoding RNAs can be classified into various types, including snoRNAs, microRNAs (miRNAs), small interfering RNAs (siRNAs), and long noncoding RNAs (lncRNAs).Among them, small nucleolar RNAs (snoRNAs) mainly participate in rRNA modification, including 2'-O-methylation and pseudouridylation; microRNAs (miRNAs) inhibit translation through incomplete complementary pairing with target mRNAs or lead to mRNA degradation through RNA interference (RNAi) mechanisms; small interfering RNAs (siRNAs) lead to the degradation of target mRNAs through RNAi mechanisms; and long noncoding RNAs (lncRNAs) regulate gene expression at multiple levels, including chromatin structure, transcription, RNA splicing, editing, translation, and degradation (21, 22).

MicroRNAs

MicroRNAs (abbreviated miRNAs) are small single-stranded noncoding RNA molecules (containing approximately 22 nucleotides) that function in RNA silencing and posttranscriptional regulation of gene expression. miRNAs work by base-pairing with complementary sequences in mRNA molecules. This causes these mRNA molecules to be silenced by cleaving the mRNA strand into fragments, destabilizing the mRNA by shortening its poly(A) tail, and having ribosomes translate the mRNA into proteins less efficiently (23, 24). The expression of miR-16, miR-29a/b-1, and miR-195, which are downregulated in AD patients and AD mice models, primarily reflects the role of miRNAs in the production and removal of Aβ.16 It has been demonstrated that miR-16 can lower the total phosphorylation level of tau protein and control the expression of APP and BACE1, which lowers the formation of Aβ (25). In the population with increased BACE1 expression, the expression of miR-29a and miR-29b-1 is considerably lower in the brains of AD patients.Patients with mild cognitive impairment (MCI) and early AD patients who carry a single ApoE ε 4 allele had lower expression of miR-195. Additionally, it can lower Aβ synthesis by controlling PIP2 and synaptophanin1 (synj1) expression (26).

Long chain noncoding RNAs and AD

The role of long noncoding RNAs (lncRNAs) in AD is an emerging research field. The lncRNA BACE1-AS can raise BACE1 levels and Aβ generation by stabilizing BACE1 mRNA and blocking its binding to miR-485-5p (27). Due to its increase in serum samples from AD patients and brain tissues from transgenic AD mice, it not only encourages autophagy-mediated neuronal destruction but also functions as a biomarker for disease diagnosis (28). Certain long noncoding RNAs (lncRNAs), such MEG3, are downregulated in AD models. By inhibiting astrocyte activation, their overexpression can lessen neuronal damage via the PI3K/AKT pathway (29, 30).

Gene therapy in neurodegeneration

The significant shift in the field of LOAD from ongoing inability of conventional small-molecule pharmacotherapies to change the course of the disease towards gene-based interventions is due to physiologic limitation, blood brain barrier (BBB). The included studies show that viral-mediated platforms, particularly Adeno-associated virus (AAV) serotypes, can achieve highly localized and sustained therapeutic concentrations within affected regions like the hippocampus and entorhinal cortex,whereas systemic administration of conventional drugs frequently results in poor central nervous system (CNS) bioavailability and significant off-target effects (31, 61). Moreover, the scientific justification for gene therapy in LOAD is based on its unmatched precision, especially with regard to allele-specific targets.Traditional inhibitors are not sensitive enough to differentiate between the neuroprotective APOE\epsilon2 or neutral APOE\epsilon3 variations and the pathologically significant APOE\epsilon4 isoform.On the other hand, the data gained from recent research highlights the effectiveness of CRISPR-based systems and Antisense Oligonucleotides (ASOs) in selectively silencing toxic gain-of-function alleles without interfering with vital physiological processes. Because epigenetic changes like DNA hypermethylation and histone deacetylation are intrinsically reversible, gene

therapy offers a special method for "transcriptional resetting." This precision also extends to the epigenome (62). These systems seek to restore the brain's homeostatic gene expression by providing epigenetic editors to erase inhibitory tags from suppressed neuroprotective genes, going beyond symptomatic treatment to a paradigm that really modifies illness (32, 33).

Gene delivery platforms

Adeno-Associated Virus (AAV) is a small, non-enveloped virus belonging to the Parvoviridae family. It is currently the leading platform for in vivo gene delivery, particularly in neuroscience and neurodegenerative disease research (. AAV is made up of an icosahedral protein capsid that is roughly 25–26 nm in diameter and encircles a 4.7 kb single-stranded DNA (ssDNA) genome of about 4.7kb (34). Inverted Terminal Repeats (ITRs) surround the two open reading frames in the wild-type genome, rep (replication) and cap (capsid). The therapeutic expression cassette replaces the viral genes in recombinant AAVs (rAAVs) used for treatment, leaving just the ITRs for packaging. Alternative viral vectors, such the recombinant adeno-associated virus vector (rAAV), have been developed for use in neurodegenerative illnesses like AD. Genetic material is integrated into the chromosomal DNA in the rAAV. It has been demonstrated that this vector is safe, only mildly immunoreactive, selective, and has long-term expression. It can infect nondividing neurons (1, 35).

Gene therapy targets In LOAD

The biggest genetic risk factor for late-onset Alzheimer's disease (LOAD) is the Apolipoprotein E ε4 (ApoE ε4) allele, which codes for ApoE4. According to new epidemiological data, ApoE4 affects the accumulation and clearance of β-amyloid (Aβ), which in turn causes AD (36, 37). The use of CRISPR/Cas9 technology to create stem cells for AD-related gene repair has also advanced significantly.Researchers have discovered that CRISPR/Cas9 has a very high accuracy rate in repairing genes that cause disease, and that changing APOE4 to APOE3 in iPSCs with the APOE4 allele significantly lessens the cells' AD-related characteristics. Tau protein phosphorylation and ERK1/2 phosphorylation were lower in edited neurons compared to unedited APOE4 neurons in experiments where the APOE4 gene was edited with CRISPR/Cas9 and converted to APOE3 in iPSCs from patients with sporadic AD. Additionally, edited neurons demonstrated a decrease in isoform-dependent phosphorylated tau protein release. The study found that when the APOE4 allele was changed to the APOE3/3 genotype in iPSCs from two AD patients using CRISPR/Cas9, the edited neurons did not exhibit significant differences in Aβ42 secretion levels compared with unedited APOE3 neurons. These results indicate that the combination of CRISPR/Cas9 with stem cells has great potential for the diagnosis and treatment of AD (38, 39).

NGF administration is one strategy that has started clinical testing. The first ex vivo gene therapy trial aimed at AD was finished in 2003 (40, 65). The findings of this work served as the basis for later research using an adeno-associated virus (AAV) vector that encoded the gene for nerve growth factor (NGF), a protein that promotes the survival and proper operation of cholinergic neurons. This was the first extensive, multi-center investigation of gene therapy for AD. Its findings prompted more research.

Patients with mild to moderate AD received intracerebral injections of the AAV2 adenovirus containing the NGF gene (CERE-110) into the basal nucleus of Meynert (an region badly impacted by AD) in a 2010 clinical trial (41). In this trial, patients who got CERE-110 did not significantly delay the progression of their disease when compared to those who received a placebo (42).

Challenges and limitations

Blood-brain barrier and delivery barriers

This section summarizes how the blood-brain barrier (BBB) permeability makes it difficult to deliver drugs and genes to the brain. Novel therapies must consider the delivery of multiple therapeutic factors without exposure to non-target genes, efficient bypass of the BBB, and the efficacy and safety of therapeutic drugs. Limited drug penetration through the BBB prevented medication trials from reaching the central nervous system. Due to this restriction, a higher dosage was required, increasing the likelihood of secondary side effects. Some therapies, including HDAC2 inhibitors, showed limited BBB permeability. However, there is a possibility for these drugs to have serious adverse effects. Drug therapies such as exosomes and liposomes were proposed to improve brain accessibility. These drugs improved cognition and behavior but did not stop disease progression. Extracellular vesicles can transport nucleic acids, proteins, and mitochondria that can be administered intranasally or inhaled to cross the BBB. However, safety concerns remain unresolved (43, 44).

Safety and immunogenicity

The findings showed serious immunogenicity issues that triggered immune responses and systemic adverse effects, including neuroinflammation of brain tissue. The use of gene therapy may result in antagonistic epigenetic changes and unintended alterations in gene expression, causing serious side effects. In mice, a recently developed HDAC inhibitor reduces tau protein phosphorylation, which decreases amyloid-beta levels. The patient's immune system produced antibodies using vaccination techniques. Meningoencephalitis occurred in 6% of participants as a result of severe immune responses and autoimmune reactions. (45, 46). An active vaccine using synthetic amyloid-beta showed reductions in plaque and improved cognition. However, the outcomes were limited by safety concerns. Long-term use of HDAC inhibitors may raise safety concerns because of their lack of isoform specificity. This raises the possibility of serious systemic adverse effects. The nuclease-deficient CRISPR/Cas9 therapeutic approach binds to specific regions without cleaving them. These approaches were successful in lowering amyloid beta levels and enhancing cognitive function. Different parts of a single gene may undergo opposing epigenetic changes. These risks may narrow the therapeutic window due to potential immune reactions and other side effects (47, 48, 60).

Ethical considerations

Patients using these medications needed to be regularly assessed and checked for adverse effects such as bleeding or swelling. Moreover, some antibody-based therapies require genotyping resources and genetic consultation, and regular MRI monitoring to detect side effects. The high expense, the need for healthcare resources, the uncertain clinical benefit, restricted access and treatment equity were further

problems. Ethical and clinical implementation challenges also depend on detailed knowledge of the natural history of the disease and the selection of the patient population, which are crucial to the development of disease-modifying therapies (49, 50).

Discussion

Translational significance of epigenetic findings

The translational potential of LOAD epigenomics rests on two properties that distinguish epigenetic modifications from conventional genetic risk variants. The first is their reversibility: unlike a nucleotide substitution or a copy-number variant, a methylated cytosine or a deacetylated histone can in principle be chemically restored to its physiological state, either by endogenous enzymatic reversal or by pharmacological or gene-based intervention. The second is their accessibility: epigenetic marks are not confined to the brain but appear, in modified form, in blood, saliva, and other easily sampled peripheral tissues, making them candidates for minimally invasive biomarker development (51, 52). These properties, taken together, mean that epigenetic research in LOAD is not purely descriptive — it generates leads that are actionable both diagnostically and therapeutically (53, 59).

How can gene therapy target LOAD epigenetic dysregulation

That epigenetic modifications are chemically reversible has always been the conceptual foundation for their therapeutic appeal, but the actual translation of this principle into viable neurological interventions has proven considerably more demanding than early optimism suggested. The challenges are not trivial: the brain is immunologically privileged, pharmacologically difficult to access, and composed of highly specialised, post-mitotic cell populations that respond to perturbation differently from rapidly dividing tissues. Nevertheless, the past decade has seen meaningful convergence of three therapeutic modalities — small-molecule epigenetic drugs, targeted nucleic acid approaches, and precision epigenome editing — each offering a distinct risk-benefit profile and mechanistic scope (53, 54, 55).

Current clinical evidence and ongoing trials

The clinical evidence base for epigenetic interventions in LOAD is, by any candid assessment, still at an early stage. Preclinical findings have accumulated rapidly, but the translation of those findings into human trial data has been slow, partly for biological reasons — the target engagement and pharmacodynamic monitoring of epigenetic compounds in the living human brain is technically demanding — and partly because the AD clinical trial enterprise has been disproportionately focused on amyloid-clearance strategies for most of the past two decades. The 2025 snapshot of the AD drug development landscape documented 182 active clinical trials evaluating 138 distinct agents, of which epigenetic modulators constitute a discernible and growing, if still modest, fraction (56). This growth occurs against the backdrop of a historically sobering failure rate: across the decade from 2002 to 2012, the attrition of AD drug candidates reached approximately 99%, a statistic that has driven the field toward earlier intervention, biomarker-stratified enrolment, and a broader exploration of disease

mechanisms beyond amyloid clearance — the latter opening a wider door to epigenetic approaches (57, 58).

Research gaps and future directions

Progress in LOAD epigenomics has been real and in places impressive, but an honest accounting of the field reveals persistent gaps at every level — from the fundamental interpretation of epigenetic data to the translational infrastructure needed to convert mechanistic insights into clinical interventions. Addressing these gaps is not simply a matter of accumulating more data of the same kind; in several instances, it requires methodological reorientation (66, 67). The single most consequential unresolved question in LOAD epigenomics is whether the methylation and histone modification changes that have been reproducibly documented are causal contributors to disease onset and progression, or whether they arise downstream of pathological processes initiated by other mechanisms. The fact that some DMPs are detectable in presymptomatic tissue is suggestive of causality, but it does not establish it: a modification that precedes clinical symptoms may still be driven by subclinical amyloid or tau accumulation rather than being an independent upstream driver (35, 49, 68).

Finally, the clinical deployment of epigenetic biomarkers will require a degree of methodological standardisation that the field has not yet achieved. Different methylation array platforms, bisulfite conversion protocols, preprocessing pipelines, and reference populations generate results that are not directly comparable across laboratories, and the reference ranges required for individual-level clinical interpretation have not been established for most candidate markers. Investment in harmonised measurement standards, certified reference materials, and cross-platform validation studies is unglamorous but essential (69, 70). The tissue-specificity problem — the imperfect correspondence between brain and peripheral methylation — may ultimately be partially resolved through analysis of methylation signatures in extracellular vesicles derived from neural cells or through direct methylome profiling of CSF cell-free DNA, both of which offer closer approximations of central epigenetic states than bulk blood (Villa & Combi, 2024). The regulatory approval in 2025 of the first blood-based diagnostic test for AD, measuring plasma phospho-tau 217, demonstrates that the FDA pathway for fluid biomarkers in this disease context is navigable and that clinical appetite for minimally invasive diagnostic tools is substantial — a regulatory and commercial template that the epigenetic biomarker field would do well to study and emulate (71, 72).

Conclusion

Looking forward, the priorities that emerge most clearly from this synthesis are precision, inclusivity, and mechanistic rigour. Therapeutic development in LOAD must move decisively away from population-level treatment averages toward individualised strategies that are anchored in a patient's specific genomic, epigenomic, and biomarker profile — a vision whose feasibility is supported by the methylomic subtyping work that has already identified at least two biologically distinct LOAD subtypes with different pathway vulnerabilities (PMC9953731, 2023; Villa & Combi, 2024). Epigenetic mechanisms deserve particular investment in this context precisely because of their reversibility: unlike fixed DNA sequence variants, aberrant methylation patterns and histone modification states are

in principle correctable, offering a therapeutic window that genetic approaches cannot access (Thakur et al., 2023; Wood, 2018). The emergence of RNA-based therapeutic modalities — including antisense oligonucleotides targeting BACE1-AS and other disease-relevant lncRNAs, and miRNA mimics or inhibitors designed to restore dysregulated small RNA networks — alongside CRISPR/dCas9-mediated epigenome editing strategies such as the APOE-ε4-selective silencing system developed at Duke University, already provide concrete proof-of-concept evidence for what mechanistically precise epigenetic treatment might look like in the LOAD context (Kantor & Chiba-Falek, 2024; Tiwari et al., 2025; Park et al., 2025). These approaches are not yet clinically mature: reliable, cell-type-selective delivery across the blood-brain barrier remains an incompletely solved engineering challenge; the target specificity of epigenome editing tools must be demonstrated rigorously in primate models before human application is justified; and the long-term safety profile of durable epigenetic silencing in post-mitotic neurons — where off-target modifications cannot be diluted through cell division — requires empirical characterisation that current datasets do not yet provide (Park et al., 2025; Kantor & Chiba-Falek, 2024). These are real obstacles, but they are the kind of tractable technical and regulatory challenges that a well-resourced and strategically coordinated research effort can address, rather than fundamental scientific barriers to the approach. Progress across demographically inclusive longitudinal cohorts, multi-omic data integration platforms, biomarker-driven clinical trial designs, and precision delivery technologies will, in combination, be the determinants of whether the theoretical promise of epigenetic medicine in LOAD is converted into the earlier diagnoses, more effective interventions, and equitably distributed clinical benefit that the scale of this disease demands.

During the preparation of this work, the author(s) used Grammarly AI and Google Gemini. The application of these tools was strictly limited to improving grammar, spelling, style, and formatting. All intellectual content is the original work of the authors.

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Abbreviations
Alzheimer's Disease (AD)
Late-onset Alzheimer's Disease (LOAD)
Clustered regularly interspaced short palindromic repeats (CRISPR)
Adeno-associated virus (AAV)
DNA methyltransferase (DNMT)
Histone deacetylase (HDAC)
Histone acetyltransferase (HAT)
Histone methyltransferase (HMT)

Ten-eleven translocation (TET)
Sirtuin (Silent information regulator) (SIRT)
MicroRNA (miRNA)
Long non-coding RNA (lncRNA)
Circular RNA (circRNA)
Small interfering RNA (siRNA)
RNA interference (RNAi)
Apolipoprotein E (APOE)
Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1)
Amyloid-beta (Aβ)
Neurofibrillary tangle (NFT)
Blood-brain barrier (BBB)
Single-nucleotide polymorphism (SNP)
Genome-wide association study (GWAS)
Epigenome-wide association study (EWAS)
Differentially methylated region (DMR)
Histone deacetylase inhibitor (HDACi)
S-adenosylmethionine (SAM)
S-adenosylhomocysteine (SAH)
Methyl-CpG-binding domain (MBD)
Protein-protein interaction (PPI)
Transcription activator-like effector nuclease (TALEN)
Zinc finger nuclease (ZFN)
Next-generation sequencing (NGS)
Induced pluripotent stem cell (iPSC)
Brain-derived neurotrophic factor (BDNF)
Nerve growth factor (NGF)
Reactive oxygen species (ROS)
Polycomb repressive complex (PRC)
Epigenetic clock (DNAmAge)
Transcription start site (TSS)
High-throughput screening (HTS)
Therapeutic window (TW)