

Advances in Gene Therapy Targeting the PSEN Gene and the BDNF Signalling in Dementia

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Received: 16th August, 2026; Revised: 8th September 2026; Accepted: 19th September, 2026; Available Online: 20th September, 2026

Abstract

Dementia is a progressive neurodegenerative disease defined by cognitive decline, neuronal dysfunction, and impairment in daily functioning. Genetic factors are of great importance in several forms of dementia, especially in early-onset familial Alzheimer's disease (AD). Presenilin 1 (PSEN1), presenilin 2 (PSEN2) and brain-derived neurotrophic factor (BDNF) are important molecular targets because they are involved in amyloid processing, neuronal survival, synaptic plasticity, learning and memory. This review addresses the role of PSEN genes and BDNF signalling in dementia and assesses emerging gene-based therapeutic approaches. Published literature was reviewed in a narrative way with a focus on pathogenic PSEN mutations, BDNF alterations and polymorphisms, molecular mechanisms related to neurodegeneration and preclinical gene-delivery approaches. The evidence considered suggests that PSEN1 mutations can affect the processing of the amyloid precursor protein by γ -secretase and thereby contribute to amyloid disease. PSEN2 mutations show variable toxicity and disease penetrance. Decreased BDNF expression has been associated with dementia, impaired neuronal and synaptic function, and other neurological disorders. The preclinical studies of BDNF gene transfer have demonstrated enhanced synaptic function and implications for learning, memory and behaviour. These findings highlight the potential of PSEN/BDNF-targeted gene therapy as an emerging approach for dementia. However, there are still challenges in efficient delivery, control of gene expression, limitations of the blood-brain barrier and long-term safety. Further preclinical and clinical studies are required to confirm the therapeutic efficacy and safety of these strategies.

Keywords: Alzheimer's disease, Dementia, BDNF, PSEN1, PSEN2 and Gene therapy.

How to cite this article: Saraswat N, Mahima, Pandiyarajan R, Singh BP, Chandra S., Advances in Gene Therapy Targeting the PSEN Gene and the BDNF Signalling in Dementia. Int J Drug Deliv Technol. 2026;16(84s): 1875-1902; DOI: 10.25258/ijddt.16.84s.190

1. Introduction

By 2050, experts predict that there will be 100 million people living with dementia worldwide, a figure that is rapidly increasing due to the increasing frequency of the disease. Caring for people with dementia is becoming more expensive and is putting a significant strain on economies around the globe(1). A person is said to be suffering

from dementia if they are unable to carry out their everyday tasks due to a progressive decline in cognitive abilities such as thinking, remembering, and reasoning. Personality changes and inability to regulate emotions are symptoms of dementia(1)(2). The severity of dementia varies from the initial stage, when it barely affects a person's ability to function, to the advanced stage, where the person is

totally dependent on others for basic daily tasks like feeding themselves. Although “Alzheimer's disease” (AD) accounts for the vast majority of cases of dementia, there are a number of other forms, such as “frontotemporal dementia” (FTD), “Lewy body dementia” (LBD), and “Parkinson's disease dementia” (PDD)(3). Although getting aged is the main cause of dementia, heredity is a major component in the development of some forms of the disease, particularly those with an early start or inherited patterns(4)(5).

Progress in genetic testing and “Genome-wide association studies” (GWAS) has facilitated the identification of more genes linked to various forms of dementia. Gene therapy and precision medicine are new areas of dementia research. These are all designed to modify or regulate the expression of harmful genes, slow the rate of dementia and perhaps even reverse dementia-related loss of cognitive function(6)(7).

There are emerging areas in dementia research, such as gene therapy and precision medicine. These strategies aim to modify or regulate the expression of harmful genes, slow cognitive decline, and perhaps even reverse it. “Brain-derived neurotrophic factor (BDNF)” is an important factor in the context of dementia, as it is important for maintaining brain health and cognitive function. The neuronal processes necessary for learning and memory—survival, development, and plasticity—are aided by BDNF(8). In individuals with dementia, particularly AD, BDNF is reduced and is linked to loss of synapses, memory loss, and increased neurodegeneration. Cognitive decline is worsened by a decrease in BDNF, which hinders the brain's capacity to recover from harm and adapt(9).

Moreover, the BDNF is involved in the brain's response to amyloid-beta (A β) and tau proteins, two pathological markers of AD. Lower BDNF levels are associated with increased Amyloid toxicity, Tau hyperphosphorylation and neuroinflammation(10). A common genetic variant of the BDNF gene (often called Val66Met) has been linked to a higher risk of late-onset AD and lower memory function. BDNF is investigated as a therapeutic target because of its protective and regulatory functions, and interventions such as physical exercise, dietary changes and pharmaceutical drugs have been proposed to promote the expression of BDNF to prevent or slow the progression of dementia(11).

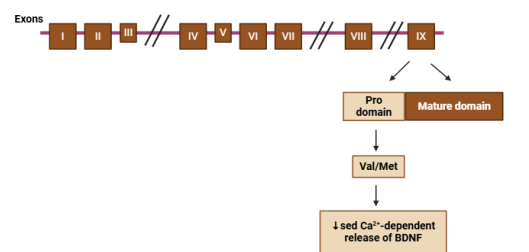


Figure 1: The length of BDNF is around 67 kb, and it has 11 exons. The change from valine to methionine in the prodomain is accompanied by a decrease in BDNF release that is dependent on calcium.

“Presenilin 1 (PSEN1)” and “Presenilin 2 (PSEN2)” are two important genes that contribute to the progression of familial Alzheimer's disease (FAD), especially the early-onset variant(12). The complex known as the γ -secretase is in charge of digesting the amyloid precursor protein (APP), and both genes encode proteins that are essential components of this complex. A characteristic aspect of AD pathogenesis is the accumulation of toxic peptides into plaques, and mutations in PSEN1 and PSEN2 change this processing, resulting in an increase in the generation of A β 42(13)(14). The majority of cases of early-onset FAD are caused by mutations in the protein PSEN1, which usually leads to a quick deterioration in cognitive abilities and neurodegeneration. Although not as common as those of PSEN1, mutations in PSEN2 are also associated with Parkinsonism and other neurological disorders(15). Presenilins have been implicated in a variety of processes that are disrupted in dementia, such as amyloid metabolism, calcium homeostasis, cell signalling and neuronal survival. Thus, PSEN1 and PSEN2 dysfunction may lead to widespread damage of neurons and impaired function of synapses, and this may result in progressive memory loss. They play a key role in genetic and sporadic AD and are important targets for understanding the disease and possible therapies(16).

Understanding the underlying genetic mechanisms of dementia will be key to developing better diagnostic tools, treatments and prevention strategies. While genes play an important role in many dementias, it is often a combination of genes and environmental factors that determines whether a person will develop dementia or not. Current research is elucidating the intricate genetic determinants associated with dementia, advancing our pursuit of more personalised and focused

therapy strategies. This review addresses the role of PSEN genes and BDNF signalling in dementia and assesses emerging gene-based therapeutic approaches.

2. Genetic basis of Dementia

2.1 Genetic Basis of Alzheimer disease

AD is the predominant neurodegenerative condition in the elderly and the leading cause of dementia overall. The principal neuropathological features in AD are amyloid plaques formed by β -amyloid and neurofibrillary tangles comprised of tau protein. AD is probably attributable to a confluence of hereditary and environmental influences. AD is often classified into early-onset AD (EOAD; onset < 60 years) and late-onset AD (LOAD; onset > 60 years)(17).

Researchers noted that within families with EOAD, which constitutes 1 to 5% of cases, a considerable proportion exhibited autosomal dominant inheritance. This facilitated the successful application of linkage analysis to identify the causal genes presenilin 1 (14q24.2) and presenilin 2 (1q42.13)(18). The predominant mutations associated with EOAD are located in the PSEN1 gene. Over 300 mutations (221 hazardous) of the PSEN1 gene and 80 mutations (19 hazardous) of the PSEN2 gene have been documented. These mutations have been associated with the onset of FAD(19). The PSEN gene range encompasses missense mutations, deletions, minor insertions, and genomic deletions, particularly in PSEN1. PSEN1 mutations result in the most severe forms of AD with total penetrance, with onset potentially occurring as early as 25 years of age(20). PSEN2 gene missense mutations may show incomplete penetrance, resulting in carriers having a later onset of disease than persons with PSEN1 mutations. Missense mutations result in mutated proteins that disrupt the function of the γ -secretase complex and subsequently affect the processing of APP, leading to an elevated A β 42/A β 40 ratio(21)(22). While the majority of LOAD patients lack a distinct heritable aetiology, genetic factors still significantly influence illness risk. The lifetime risk of developing AD is approximately 10%, which doubles for persons with an affected first-degree relative with AD. Research has estimated that the genetic influence on LOAD susceptibility (i.e., heritability) may reach as high as 80%. It is noteworthy that no individual gene has been identified as having a causal influence on disease

risk in LOAD, unlike the function of PSEN1 or PSEN2 in EOAD(23).

On the other hand, the BDNF gene has been linked to preventing the development of two important components in the pathophysiology of AD— β -amyloid plaques and neurofibrillary tangles(24). In addition, BDNF shields neurons from the A β peptide's neurotoxicity and the death of neurons caused by the aggregation of A β and Tau proteins in AD(25). Researchers have also found that BDNF is essential for the survival and proper functioning of the disease's terminally degenerating neurons. Brains of AD patients show a significant decline in BDNF mRNA and protein, including pro-BDNF(26). BDNF shields neurons from the A β peptide's neurotoxicity and the death of neurons caused by the aggregation of A β and Tau proteins in AD. Researchers have also found that BDNF is essential for the survival and proper functioning of the disease's terminally degenerating neurons (25)(27). Further, research has shown that AD patients' frontal brain and hippocampus have lower amounts of BDNF and its receptor, tyrosine kinase B. The deterioration of the hippocampal network is the most noticeable pathological feature of AD, and BDNF is a great choice for screening due to its protective role in reducing amyloid-related damage(28). In this context, it has been reported that rs6265 on the BDNF gene controls the correlation between β -amyloid and hippocampal disconnection in AD, indicating that the protein plays a significant role in the pathogenesis of the disease(29). In addition, early-stage AD patients show a reduction in parietal cortex and hippocampal levels of mature BDNF and its messenger RNA. Furthermore, there is a correlation between the severity of this disease with serum BDNF levels(30).

2.2 Genetic Basis of Dementia with Lewy bodies

“Dementia with Lewy Bodies” (DLB) is caused by protein accumulation in your nerve cells. The brain's chemical communications are disrupted by these deposits, leading to disorientation and memory loss(31). There is a high degree of overlap between DLB and disorders like Alzheimer's and Parkinson's. Many people, for instance, experience weakness, shakiness, and tremors in their hands and feet(32). A defining characteristic of these associated illnesses is the intraneuronal cytoplasmic inclusion termed the Lewy body (LB), whereby α -synuclein serves as the principal aggregated protein. LBs may be found in the brains

of individuals with AD and frequently in those with PD as well(33). In PD, LBs are predominantly localised in the substantia nigra and specific areas of the brainstem. In DLB, the LBs are extensively distributed throughout the cerebral cortex and are linked to the diverse cognitive and psychiatric manifestations of DLB, including progressive cognitive deterioration, visual hallucinations, and varying levels of attention and alertness(34). The majority of DLB cases are non-familial. The gene most closely associated with familial DLB is the one that encodes α -synuclein. Gene triplication is linked to PD and DLB. Infrequent autosomal dominant mutations in synuclein can lead to familial PD, characterised by a significant presence of dementia. Mutations in glucocerebrosidase associated with PD may also have a role in DLB(35). In 2008, a proband with DLB symptoms was found to have a PSEN2 missense mutation. The mutation was a C-to-T change at the second position of codon 85, which results in a change from alanine to valine in the produced protein. Neuropathological evaluation of the proband showed an abundance of AD-related lesions and cortical LBs. Within his family, six carriers were found over two generations; each of these carriers had a unique set of symptoms.

Except for one young, asymptomatic relative, every single person who carried the A85V mutation eventually suffered from AD, DLB, or both. There were no further mutations in AD-related genes in any of the participants(36). Like the A85V mutation in PSEN2, the harmful A79V mutation in PSEN1 is homologous. The A85 residue is highly conserved, according to the sequence's phylogenetic analysis. This mutation is located on the cytoplasmic N-terminal side of the protein, close to the TM-I domain, which could be crucial for its function. It is expected that the A85V mutation will cause disease(36)(37).

It has been found that α -synuclein problematic structures are linked to PSEN2 A85V regardless of the ApoE ϵ 4 allele, as all family members with PSEN2 A85V had a "apolipoprotein E (ApoE)" genotype of ϵ 3/ ϵ 3(38)(39). A European patient with cognitive decline and extrapyramidal symptoms, who was likely misdiagnosed with DLB, was found to have a PSEN2 mutation, R71W. An unidentified kind of dementia was also suffered by one of the proband's brothers who possessed the R71W gene(40). There was no PSEN2 mutation in the second brother, and he was healthy. It was

previously known that the R71W mutation was probably deleterious in AD patients(40)(41).

A patient with DLB who had no history of neurological problems and was experiencing extrapyramidal symptoms such as a modest resting tremor in the left arm, postural tremor in both upper limbs, and bradykinesia on the left side was found to have a PSEN2 mutation, R62H. This change, which is located at the very end of PSEN2, is shared by both PSEN1 and PSEN2. A β 42 levels and the A β 42/A β 40 ratio were not affected by the R62H mutation, as Walker et al. proved(42). To prove that the R62H variant is likely harmless, Guerreiro et al. used PolyPhen-2. Based on these findings, PSEN2 R62H is probably safe to call "not pathogenic." The R62H mutation appears to act as a disease modifier, as carriers have an earlier age of onset compared to affected non-carriers, even when adjusting for ApoE genotype(43).

Recent studies have demonstrated that BDNF could serve as a biomarker/target for DLB. A study that compared blood BDNF levels among neurological disease categories found that DLB patients had significantly lower blood BDNF levels than healthy controls, similar to previous studies in AD and FTD(44). The decrease in BDNF levels indicates a shared neurodegenerative mechanism throughout various dementias. Experimental studies have further clarified the involvement of BDNF in DLB. This BDNF-transplanted neural stem cell (NSC) group in a transgenic mouse model of DLB showed significant improvements in cognitive and motor functions. These improvements were associated with the recovery of dopaminergic and glutamatergic signalling pathways, which are crucial for functional recovery of the brain. Importantly, these therapeutic benefits were not reproduced in the absence of BDNF expression in NSCs, underscoring the importance of BDNF in providing these benefits. Another genetic variant (the BDNF Val66Met polymorphism) has been associated with a higher risk of DLB development(45)(46). This polymorphism may be involved in the pathogenesis of the disease and in the course of the illness and may also be related to the synaptic plasticity and hippocampal activity. All of these results point to BDNF as a key player in the pathophysiology of DLB. The importance of BDNF in DLB is highlighted by the reported decrease in the levels of BDNF and the therapeutic potential of BDNF-based therapies. Further research on the role of BDNF could lead to new

diagnostic and therapeutic strategies that aim to decrease the mental and physical dysfunction associated with DLB(47).

2.3 Genetic Basis of Parkinson's disease dementia (PDD)

The Parkinson's Foundation estimates that up to 70% of individuals with PD will eventually acquire dementia, while more recent research indicates that the number may be lower. Reasoning and judgment issues are early indicators of this kind of dementia(48). For instance, a person with PDD may struggle to remember basic daily duties or to comprehend visual information. They might even have frightening or confusing hallucinations. Irritability is another symptom of PDD. As the illness worsens, many patients experience paranoia or depression(49). Others may have trouble speaking, lose words, or become disoriented during a conversation. Postural instability and gait disruption are a group of motor impairments that are a unique risk factor for PDD. This includes having trouble balancing and falling, starting to move, and shuffling(50). During the last years of PDD, a 77-year-old PSEN2 V191E carrier displayed the PDD phenotype, which is marked by cognitive impairment, visual hallucinations, and confusion. The protein's highly conserved amino acid residue is where this PSEN2 mutation is found. Bram Meeus predicted that the V191E mutation is harmful because it was absent in over 1,200 control subjects in his study(51).

A Swedish PD family has been reported to have a de novo α -synuclein A53T mutation together with a PSEN2 R163H variation. Although she was healthy, the proband's mother likewise had the PSEN2 R163H mutation. However, when combined with α -synuclein, this mutation cannot be ruled out as a cause of PD(52).

Recent studies also shed light on the function of BDNF in PD, particularly as it relates to dementia and cognitive decline. The concentration of BDNF, a neurotrophin that promotes synapse plasticity and neuronal survival, may be a biomarker of neurodegenerative processes(53). The Jiang et al. (2023) Meta-analysis showed that the serum BDNF level in PD patients was significantly lower than in healthy controls. Given that this reduction was observed across the entire cohort of PD patients, regardless of whether they had depression or not, it is plausible that the decrease in BDNF is not necessarily due to depression, but is instead due to PD itself(54). Furthermore, Wang et al. (2016)

found that cognitive dysfunction in PD patients was correlated with a decline in the serum BDNF level. Cognitive abnormalities in PD are related to reduced BDNF, as indicated by the positive correlation between BDNF levels and "Repeatable Battery for the Assessment of Neuropsychological Status" (RBANS) scores. These findings together suggest that the cognitive decline in PD patients is associated with reduced BDNF levels, and monitoring the levels of BDNF could be a potential biomarker for assessing cognitive functioning in PD patients(55).

2.4 Genetic Basis of Frontotemporal dementia

After AD, FTD, a clinical manifestation of frontotemporal lobar degeneration, is the second most prevalent type of neurodegenerative illness with an early onset (less than 65 years). Deterioration of behaviour, personality, and language skills are its primary characteristics(56). FTD accounts for 10% to 30% of all cases of presenile dementia. FTD can lead to obsessive behaviour and a loss of drive and inhibitions. Additionally, it creates speech issues, such as forgetting the meaning of familiar words(57). Compared to Alzheimer's, FTD may have more severe speech impairments. In contrast to Alzheimer's, FTD-related memory issues typically manifest later in the course of the illness. A greater proportion of FTD is "genetic" than AD(58). About 10–20% of people with FTD follow an autosomal dominant pattern of inheritance, and nearly 50% have a positive family history. There have been reports of clinical and molecular similarities between AD and FTD or FTD-like traits. In patients with FTD, at least four PSEN2 mutations have been discovered thus far. A 31-year-old patient was discovered to have PSEN2 R62H in 2010. This mutation was also present in the patient's healthy mother. The combination of the ApoE ϵ 2 allele and the H1 MAPT haplotype may act as a protective modifier against FTD, but the H1 MAPT haplotype alone may increase the risk of FTD. These possibilities suggest that several genes' enhancer, suppressor, and modifier effects could be important for genetic analysis(51)(59).

Recent investigations have elucidated the role of BDNF in FTD, indicating both retained and diminished amounts of this neurotrophin in varying situations. Ferrer et al. (2000) conducted a study analysing post-mortem brain samples from patients with FTD and age-matched controls. Through Western blotting and immunohistochemistry, they

determined that BDNF expression was maintained in the frontal and temporal cortices of FTD patients. This preservation was noted in the remaining neurones of both the upper and inner cortical layers, indicating that FTD is not linked to a decline of BDNF in cortical neurones(60). Research by Ventriglia et al. (2013) indicated reduced serum BDNF levels in patients with FTD relative to healthy controls. This discovery suggests that although BDNF expression may be maintained in specific brain regions, peripheral BDNF levels are diminished in FTD, indicating a complicated control of BDNF in this disorder(61).

The divergent results underscore the intricacy of BDNF regulation in FTD. Although central nervous system expression may be preserved in specific areas, peripheral BDNF levels seem to be reduced, indicating that BDNF's involvement in FTD entails complex mechanisms that require additional exploration(62).

3. Role of PSEN Genes in Neurodegenerative Processes

3.1 PSEN1 and PSEN2 Structure and γ -secretase Function

PSEN1 and PSEN2 have 66% sequence homology and are both members of γ -secretase. However, PSEN1 seems to be a more important factor in the development of AD than PSEN2(62). Nine "transmembrane domains (TM)" attached to hydrophilic loops in either the extracellular or cytoplasmic regions make up PSEN1, a transmembrane protein. The C-terminal segment is found in the extracellular compartment, while the N-terminal portion and the lengthy hydrophilic loop are present in the cytosol. A big hydrophilic loop is also a component of the domain that is related to the membrane(63).

The processing of amyloid peptides and APP rely on the γ -secretase complex, of which PSEN1 is an essential component. PSEN1 has two critical catalytic aspartic acids; one on TM6 (Asp275) and another on TM7 (Asp385), which are essential for PSEN1 endoproteolytic activity as well as for γ -secretase activity(64). Additional essential residues were identified in the transmembrane region, situated between positions 95 and 98. Alterations in these residues may hinder or eliminate PSEN1

proteolysis and γ -secretase functionality(65). Another significant residue may be Asp345, situated in the loop between TM6 and TM7. A caspase cleavage site was identified adjacent to this amino acid, which is essential for the interaction between PSEN1 and its binding partners. PSEN1 or PSEN2, as components of the γ -secretase complex, associate with "nicastrin (Nct)", "PSEN enhancer 2 (PEN2)", and "anterior pharynx 1 (APH-1)(15). Moreover, the γ -secretase complex is recognised for its interactions with several other proteins, including ubiquitin, proteins associated with folding, and adhesion molecules. PSEN1 participates in the C-terminal transmembrane domain of APP and facilitates the generation of A β 42 by γ -secretase, subsequent to APP processing by α - and β -secretases(66).

PSEN1 may not function as an enzyme, but rather serves as a vital regulatory protein in γ -secretase cleavage. PSEN1 may possibly be involved in the transfer of the C-terminal APP fragment to the γ -secretase complex. A deficit in PSEN1 function may disrupt APP processing, leading to modified amyloid peptide synthesis. Multiple presenilin domains may be crucial for protein activities(67). The C-terminal segment connects with the nicastrin protein. Furthermore, it can regulate γ -secretase activity by ATP binding at its nucleotide-binding site. Additionally, the C-terminal segment engages with TM1 and associates with APP. The N-terminal domain of PSEN1 (HL1, TM2 and TM1) is essential for the catalysis of substrates inside the γ -secretase complex. Furthermore, these domains may influence PSEN1 endoproteolysis and the alignment of substrate binding to the enzyme(68).

The interaction between TM2 and TM3 may influence the conformation of γ -secretase (either "semi-open" or "fully open") and could regulate the accessibility of the enzyme's active site. The "semi-open" conformation of the enzyme may be optimal for the synthesis of short amyloids, but mutations could prompt the

"open" conformation, resulting in the generation of longer amyloid peptides. TM5 and TM6 may facilitate endoproteolysis and the maturation of the PSEN1 protein by regulating the "gate-plug mechanism. In order to enhance the effects of γ -secretase activation and facilitate the endoproteolysis of PSEN2, the TM4 domain of PSEN1 binds directly with PSEN2(69). It is possible that amyloid cleavage does not require the N-terminal part of PSEN1 or the long loop between TM6 and TM7. Two aspartate residues that catalyse the reaction are located in the TM6 and TM7 domains. The presence of a water-filled hole in the membrane between transmembrane domains 6 and 7 allowed for hydrolysis to take place within the lipid bilayer(70).

3.2 PSEN- Mediated Notch Signalling

In addition to APP and the γ -secretase complex cleaving various substrates, PSEN1 and PSEN2 cleaving Notch receptors can also impact Notch signalling. Cell destiny, cell differentiation, and cell division are all regulated by Notch signalling(71). PSEN1 is important for Notch receptor cleavage in transmembrane areas. To facilitate its translocation into the nucleus, PSEN1 controls the release of the "Notch receptor intracellular domain (NICD)"(15).

The essential and conserved involvement of presenilin in Notch signalling has consistently demonstrated the proteolytic actions of γ -secretase. In all species, significant developmental abnormalities are linked to modified expression of Notch target genes, including the "hairy and enhancer of split (HES)" family(72). Utilising conditionally targeted alleles or partial knockouts of presenilin, along with γ -secretase inhibitors, enables the assessment of presenilin's role in Notch signalling during adulthood. Deficiencies in T- and B-cell differentiation, hemorrhagic diarrhoea due to impaired intestinal goblet cell differentiation, and dermatological and trichological abnormalities have been noted(73). Neurodegeneration progresses when presenilins in the forebrain are conditionally knocked out in the forebrain using an α CaMKII promoter to induce Cre

expression. The loss of presenilin activity may contribute to the pathogenesis of sporadic AD, regardless of its effect on A β 42 production, according to this phenomenon. It can be inferred that these mutant mice are not representative of AD due to the expected absence of A β accumulation(74). PSEN1 might regulate the stability of β -catenin, which could lead to its involvement in Wnt signalling. β -catenin phosphorylation, cyclin D1, c-Myc, and CDK6 suppression, and cell-cycle advancement can all be aided by PSEN1. Mutations in PSEN1 have the potential to directly or indirectly interfere with Wnt signalling. Apoptosis of neurones and downregulation of Wnt signalling could result from PSEN1-induced amyloid- β toxicity(75).

In contrast, PSEN1 mutations may potentially enhance Wnt signalling, resulting in improper cell cycle events and neuronal degeneration. PSEN1 modulates the trafficking and turnover of the "epidermal growth factor receptor" (EGFR). Loss or malfunction of PSEN1 has been proposed to diminish EGFR1 turnover. This mechanism hinders EGFR trafficking from endosomes to lysosomes(76). PSEN1 may influence the activation of "phospholipase C (PLC)" and "protein kinase C" (PKC). The deletion of PSEN1 and PSEN2 resulted in diminished expression of the majority of PKC and PLC isoforms. Nonetheless, PKC delta levels were elevated in PSEN1 mutant cells, leading to an increased incidence of apoptosis and diminished mitochondrial membrane potential(77).

3.3 PSEN- Associated Calcium Signalling and Cellular Dysfunction

PSEN1 may regulate calcium signalling through various PLC and PKC isoforms. PSEN1 and PSEN2 may influence synaptic homeostasis via calcium homeostasis. PSEN1 impairment may be associated with compromised synaptic dysfunctions and calcium transport(78). The function of presenilin in Ca²⁺ homeostasis remains highly debated. It is well agreed that clinical mutations in presenilin disrupt the Ca²⁺ reservoir within the endoplasmic reticulum. The processes are contested and encompass elevated expression of the Ryanodine receptor (RyR), activation of inositol-3-phosphate (IP3)-induced endoplasmic reticulum Ca²⁺

release, or activation of “sarco(endo)plasmic reticulum Ca^{2+} -ATPase” (SERCA) pumps. Presenilins may function independently as Ca^{2+} leak channels. This leakage function is exclusively observed with full-length PSEN-1 (i.e., before its incorporation into the γ -secretase complex), and PSEN-containing aspartate mutations can sustain this activity(79).

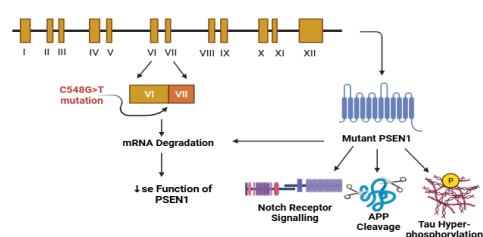


Figure 2: A simplified representation of how the mutation in Psen1 C548G>T impacts presenilin expression and function in the brain of mice. There is an acceleration of tau phosphorylation and aggregation when presenilin function is lost. Mutations in PSEN1 can result in shortened proteins that can either increase or decrease the activity of normal Notch signalling. The imbalance is shifted towards longer $\text{A}\beta$ peptides, including $\text{A}\beta_{42}$, which are more toxic and associated with AD, due to mutant PSEN1.

Numerous studies have emphasised the correlation between AD and BDNF. The diminished levels of BDNF protein and mRNA in the neocortex and hippocampus indicate that BDNF is crucial in AD. The reduction of BDNF correlates with $\text{A}\beta$ accumulation, Tau phosphorylation, neuronal apoptosis and neuroinflammation(80). Hence, if the impact of Tau pathology on neurotrophic pathways is disregarded, AD treatments that focus solely on $\text{A}\beta$ may be futile, as Tau is involved in the $\text{A}\beta$ -induced downregulation of BDNF. Additionally, the overexpression of the transcription factor C/EBP β occurs as a result of the activation of the JAK2/STAT3 pathway and the elevation of inflammatory cytokines caused by BDNF/TrkB insufficiency(81).

The elevated expression of δ -secretase results in the fragmentation of APP and Tau, ultimately culminating in neuronal death. Oxidative stress and $\text{A}\beta$ diminish PKC ϵ expression; conversely, a reduction in PKC ϵ leads to decreased BDNF and MnSOD in hippocampal pyramidal neurones, causing oxidative stress and impairing synaptic plasticity(82). Conversely, BDNF overexpression

or BDNF gene administration has demonstrated the capacity to mitigate behavioural deficits, diminish neuronal abnormalities, ease synaptic degeneration, and avert neuronal loss, while it did not influence the level of Tau hyperphosphorylation. BDNF overexpression enhances the therapeutic efficacy of transplanted “neural stem cells” (NSCs) for AD by facilitating neuronal replacement and neurogenic effects, thereby augmenting the viability of the engrafted cells, maturation of electrical properties, neuronal differentiation, neurite complexity, and synaptic density. Moreover, restricted BDNF release from astrocytes has demonstrated the ability to ameliorate memory impairments, enhance spine density, and improve synaptic characteristics(83). Moreover, BDNF-promoter methylation in peripheral blood has been examined as a predictor of AD risk. Peripheral BDNF-promoter methylation may serve as a diagnostic sign for AD risk. The cause of “amnesic moderate cognitive impairment (aMCI)” and its development into AD is influenced by the interaction between the tag SNP (rs6265) and DNA methylation (CpG5) of the BDNF gene promoter. Epigenetic biomarkers such as elevated peripheral BDNF promoter methylation may thus be useful in predicting the progression of aMCI to AD. The BDNF Val66Met polymorphism is associated with an increased risk of disease progression from “mild cognitive impairment (MCI)” to AD(84).

In contrast, the Met allele solely increased the incidence of AD in females. Similarly, there is a favourable genetic relationship of rs6265 in BDNF with AD in females, as well as a sex-related change in BDNF mRNA expression in brain regions. A substantial female-specific risk trend was observed for the influence of BDNF rs6265 on AD disease-related endophenotypes. AD and Tau pathology have also been associated with pro-BDNF, which is a form of BDNF(85). The $\text{A}\beta$ peptide and pro-BDNF interact in a detrimental way that works in tandem. This synergistic interaction is thought to be caused by $\text{A}\beta_{1-42}$ activating the BDNF pro-domain receptor p75NTR. There is a strong correlation between the pro-BDNF level and the hippocampal pTau and amyloid load. In AD brains, the ratio of pro-to-mature BDNF domains increased more than 30 times. One possible biomarker for AD is the abnormally high ratio of BDNF pro-to-mature domains in patients(86).

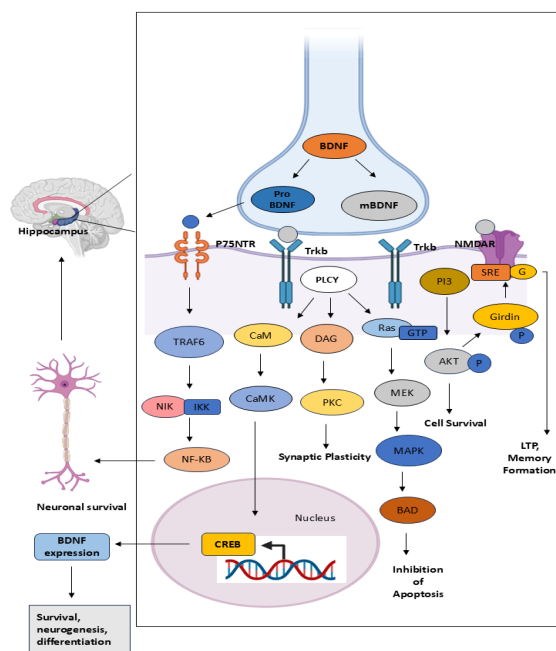


Figure 3: The mechanisms that contribute to the neuroprotective action of BDNF are illustrated in this diagram.

The reduced BDNF levels in the blood and brains of AD patients indicate that BDNF is crucial in the aetiology of the disease and may serve as a biomarker for its early identification. Depletion of BDNF correlates with neuroinflammation, A β buildup, neuronal death and Tau phosphorylation. Notably, BDNF overexpression or gene transfer has demonstrated efficacy in mitigating neural abnormalities, neuronal loss, synaptic degeneration, and behavioural impairments(87).

4. PSEN Mutations in Familial Alzheimer's Disease and their therapeutic implications

The initial advancement occurred in 1995 when two strands of genetic research converged unexpectedly, leading to the discovery of PSENs. Analysis of families with inherited forms of AD revealed mutations in the initially unidentified genes PSEN1 on chromosome 14q24.3 and PSEN2 on chromosome 1q42.2(88). A further line of genetic research in the worm *Caenorhabditis elegans* independently discovered a PSEN gene as a suppressor of lin-12 gain-of-function mutants. Lin-12 is the nematode homologue of Notch, a gene essential for cellular signalling during development(89). Consequently, PSENs played a crucial role in the pathophysiology of AD while simultaneously influencing development through the regulation of Notch signalling. Nonetheless, the relationship between these two roles remained ambiguous, and it was suggested that PSENs might

function as a receptor, channel, or transporter protein, perhaps influencing tau phosphorylation and dysfunction(90).

Presenilin mutations were initially linked to familial AD, and further research confirmed that presenilin serves as the catalytic component of the γ -secretase complex responsible for A β production. Additional research has established a strong connection between A β , particularly A β 42, and the development of monogenic, dominant familial Alzheimer's disease (i.e., in individuals with APP, PSEN2, or PSEN1 missense mutations)(91). Presenilin mutations linked to Alzheimer's disease alter the A β 42/A β 40 ratio, an important factor in the likelihood of A β to aggregate into neurotoxic forms, such as fibrillar plaques or soluble oligomers. As a result, the biochemical characteristics of the γ -secretase complex and its interaction with the APP substrate are altered by these missense mutations, leading to a preference for longer and more prone to aggregation forms of A β in transmembrane cleavage(92).

Numerous studies have demonstrated that presenilin mutations associated with AD may change intracellular calcium signalling, leading to A β aggregation, the formation of brain plaques, and neuronal cell death. Vito et al. and Wolozin et al., in separate 1996 studies, proposed that PSEN2 is involved in cell death. Scientists have shown that HEK293 human cells and murine neurones undergo p53-dependent apoptosis in response to either wild-type or mutant N141I-PSEN2. The susceptibility to staurosporine-induced cell death was dramatically amplified when PSEN2 was overexpressed in primary cortical neurones of rats. Apoptosis can be induced by mutations in PSEN2. The pro-apoptotic effects of PSEN2 can be inhibited by Bcl-2. Recent research has shown that insulin levels are decreased when mutant PSEN2 is overexpressed in humans, which changes glucose metabolism(36).

Several mutations associated with AD in presenilin lead to a decrease in total proteolytic activity, prompting the inquiry of whether a partial loss of presenilin function contributes to familial AD. Conditional deletion of PSEN1 and PSEN2 in the mouse brain induces neurodegeneration and memory impairments similar to AD, despite the absence of A β formation(93).

In contrast to APP, mutant presenilins can augment A β formation and facilitate the progression of Alzheimer's disease, whereas PSEN2 exerts a lesser influence compared to PSEN1. The quantity of

mutations detected in PSEN1 exceeds that of PSEN2. Two PSEN2 mutations, Lys306fs and Glu126fs, are frameshift mutations, while the remaining mutations are nonsynonymous replacements(94). PSEN2 mutations exhibit varied penetrance and a broad spectrum of disease onset ages, ranging from 45 to 88 years. PSEN2 mutations are linked to both EOAD and LOAD. Only 17 of the 38 are anticipated to be pathogenic mutations. Ten of the mutations are non-pathogenic, while the implications of the remaining variants remain ambiguous. Sixteen mutations are situated inside transmembrane domains(95). Cellular investigations indicate that four mutations, T122P, M239I, M239V, and N141I, elevate the levels of A β peptide. The mutations T122R, M239I and S130L were identified as modifying calcium signalling. The majority of these mutations were identified in European and African ethnicities. There is a total of four known missense mutations in Asian populations: In a Han family from China, Asn141Tyr was associated with early-onset AD; in a Japanese patient, Gly34Ser was found; and in Korean patients, Arg62Cys and Val214Leu were discovered(96).

All mutations in PSENs linked to Alzheimer's disease (over 160 found) are dominant, with a single mutant allele sufficient to induce the onset of the disease in midlife for the carrier. Moreover, none of the mutations associated with Alzheimer's disease leads to truncation or deletion of the PSEN protein; instead, the mutant protein integrates with other γ -secretase components to form fully functioning proteolytic complexes, which are consistent with normal development(97).

While numerous AD-mutant variants of PSEN1 result in diminished proteolytic activity, certain mutants exhibit only marginal decreases, if any. Furthermore, no familial AD mutations have been identified in any other γ -secretase substrate apart from APP, strongly indicating that the modification of APP proteolysis by mutant PSENs is central to the pathogenesis of Alzheimer's disease(98).

Taken together, these results suggest that presenilin mutations primarily cause FAD by a changed A β 42/A β 40 ratio. Although these mutations may not always lead to reduced proteolytic activity, none of them does in a completely inactive state. It is clear that impaired Notch signalling is a factor in the pathogenesis of AD, and the phenotypes seen in the conditional knockout mice suggest that PSENs play an important role in neuronal health or

function (e.g., neurotransmitter release) that becomes apparent only when these proteins are completely removed(97)(98).

Nonetheless, diminished activity in specific signalling pathways may serve as a secondary contributing element in EOAD cases linked to presenilin mutations, despite the absence of other recognised medical implications. The rare familial cases of Alzheimer's disease share many characteristics with late-onset sporadic AD, including a propensity to begin in middle life, a high percentage of hereditary inheritance, and a virtually comparable pattern of symptoms. Therefore, it can be inferred that A β is involved in the cause of the more common sporadic form of AD, given its clear function in familial AD(99).

The proteolysis that determines the carboxyl terminus of A β and the important A β 42/A β 40 ratio is carried out by the presenilin-containing γ -secretase complex. This protease complex is also involved in the pathogenic pathway of sporadic Alzheimer's disease. However, not enough evidence has been found to suggest that presenilin/ γ -secretase differs in structure and characteristics between non-Alzheimer's controls and sporadic Alzheimer's disease patients, or that sporadic Alzheimer's disease causes different changes in the A β 42/A β 40 ratio due to γ -secretase activity(100).

Nonetheless, it is still plausible that localised cellular alterations modify APP proteolysis by γ -secretase, resulting in the generation of elongated variants of A β . Environmental factors, such as food, may affect membrane composition, resulting in such alterations. Regardless of the eventual validation of these predictions, all A β is generated through the γ -secretase complex, rendering the protease essential to the disease mechanism. The disease process cannot occur without the γ -secretase-mediated generation of A β .

5. BDNF Signalling in Dementia and Neurodegeneration

BDNF influences gene expression, synaptic plasticity, neuronal differentiation, cell survival, neurite outgrowth, and many other CNS biological processes. The cerebellum, dentate gyrus, amygdala, cerebral cortex, and hippocampus are only a few of the brain regions where BDNF is expressed in rats and humans at variable levels(101).

The brain's "γ-aminobutyric acid-ergic (GABAergic)" and glutamatergic neurones participate in its regulation of excitatory and inhibitory synaptic transmission and synaptic plasticity. BDNF levels in brain tissues are positively correlated with serum concentrations, and it can cross the blood-brain barrier(102). Several proteases, including matrix metalloproteinases, convert the precursor proBDNF into "mature BDNF (mBDNF)" during BDNF synthesis, and then it is released into the bloodstream. ProBDNF can regulate cell death and apoptotic responses by attaching to the p75 "neurotrophin receptor (NTR)", whereas its mature version can affect neuronal survival through interaction with the "tropomyosin-related kinase B (TrkB) receptor"(103).

Anxiety, epilepsy, ischaemic dementia, cognitive impairment, hypoglycemia, and CNS BDNF levels are associated with neuropathological and neuropsychiatric symptoms. When compared to controls, individuals with mild cognitive impairment, Alzheimer's disease, and vasomotor disorders all had lower levels of CSF BDNF. In cases of moderate cognitive decline, AD, and "vasomotor symptoms (VaD)", CSF-BDNF concentrations were shown to be lower compared to control groups. People with mild cognitive impairment or decreased episodic memory function have been found to have lower blood BDNF concentrations(104).

Numerous studies demonstrate that BDNF augments presynaptic axon terminal function and affects synaptic plasticity, dendritic development, and neurogenesis, including the facilitation of "long-term potentiation (LTP)" via intercellular signalling pathways such as "glycogen synthase kinase-3β (GSK3β) signalling", as well as the preservation of noradrenergic innervations(105). ERK1/2 signalling and "cAMP-response element-binding protein (CREB)" signalling contribute to the exacerbation of depression symptoms and cognitive performance. BDNF is known to modulate synaptic strength via modulating the expression and trafficking of "N-methyl-D-aspartate (NMDA)" receptors and the complexity of dendritic spines, consequently affecting synaptic consolidation and memory formation(106).

Recent research indicates that Aβ-related neurotoxicity may result from a deficit in BDNF. Numerous studies demonstrate that the cortex and hippocampus, regions of the brain linked to

learning and memory, display significant amyloid pathology and reduced levels of BDNF in AD. Notably, BDNF protein levels are markedly diminished in the preclinical and early phases of Alzheimer's, and this decline is associated with clinical neuropsychological assessments(105).

Knowing that BDNF is essential for neuronal survival, functionality, synaptic plasticity, learning, and memory, these processes are impaired in AD; thus, it became crucial to identify the Aβ species that contribute to the decrease of BDNF in AD. In vitro evidence indicates that soluble Aβ forms diminish BDNF mRNA expression and impair BDNF intracellular signalling in both primary rat neurones and human neuroblastoma cells(107). Consequently, amyloid-induced neurodegeneration may result from diminished BDNF levels. Nonetheless, it remains unclear if Aβ assemblies downregulate BDNF in vivo and whether a specific Aβ assembly state is accountable for this downregulation of BDNF(108).

Limited research exists about factors that may alter the relationship between BDNF levels and dementia risk. Sex, smoking, and age status may correlate with BDNF levels and dementia risk; therefore, it was investigated whether they may influence the relationship between BDNF levels and the chance of developing incident dementia or Alzheimer's disease. The discovery was that elevated BDNF levels forecast a diminished risk of dementia/AD exclusively in women(109).

Among a Japanese population, only females were associated with AD when the Val66Met polymorphism in the BDNF gene was considered. New evidence suggests that plasma BDNF is a biomarker for declining memory and general cognitive function in older women, but not in men. These findings may lend credence to the theory that BDNF interacts with oestrogen and other sex hormones, or that another sex-specific mechanism plays a role in the development of AD(110).

The decline in BDNF levels that occurs with ageing may explain why the association is only seen in the elderly. Dementia and Alzheimer's disease events may arise from different pathways in younger people since they have relatively high levels of BDNF. One theory is that BDNF, which is involved in synaptic plasticity and functional efficiency, acts as a mediator between educational attainment and cognitive reserve(111). People who are more affected by BDNF may have a greater level of knowledge, but they may also be more susceptible

to the negative consequences of BDNF depletion as they get older(112).

Various studies seek to identify genetic variables linked to the onset of age-related illnesses. Consequently, polymorphisms may serve as a compelling study focus to address these enquiries. Polymorphisms of the BDNF gene are linked to dysregulation of BDNF levels. Over 100 variants of the BDNF gene have been found, with current data highlighting certain single-nucleotide polymorphisms (SNPs) that correlate positively with the manifestation of dementia-related clinical symptoms. Several of these SNPs have been extensively researched for their relationship with various illnesses(113).

Others, owing to their recent identification, lack evidence linking them to a specific condition. The SNP Val66Met (rs6265) in the BDNF gene is a change in the nucleotide at codon 66 (G/A) that changes the amino acid from Valine (Val) to Methionine (Met) in the pro-domain region of the gene(114). A change in the BDNF protein's amino acid sequence alters its regulated secretion and dendritic transport of pro-BDNF. In addition, secretory vesicles containing BDNF are connected with "Ca²⁺-dependent activator protein for secretion 2 (CAPS2)", which promotes the release of the protein, which is crucial for brain growth. When CAPS2 is present, the pro-BDNF polypeptide is released from intracellular trafficking, which is linked to the rs6265(114)(115). Therefore, people with this SNP show deficits in short-term episodic memory, underscoring the importance of the secretion of BDNF by calcium. Polymorphism is well studied and associated with many age-related disease processes such as PD, AD and depression(116). Patients with AD show a progressive loss of memory and a decrease in the size of the hippocampus, and the rs6265 SNP plays a role in this. This association is notable because this polymorphism could be a predictor for reduced memory and hippocampus volume in this patient group. There are many studies suggesting an association between the polymorphism of rs6265 and AD. In heterozygous individuals with the Met variation, there is a loss of hippocampus size and poor performance on memory tasks(117).

A separate investigation including a middle-aged group at risk for AD indicated that the presence of the BDNF Met variation correlated with a more pronounced deterioration in episodic memory and executive function. This deterioration was

intensified by an increased A β load, indicating that the rs6265 polymorphism might significantly influence cognitive decline and could serve as a potential target for innovative AD treatments(118). According to recent findings, the human BDNF gene is the site of transcription for natural antisense transcripts. Downstream of BDNF is a non-coding antisense RNA gene called BDNF-AS, which controls the BDNF gene. Evidence suggests that suppressing BDNF-AS transcription increases BDNF mRNA, which in turn increases protein levels and promotes neuronal proliferation and differentiation, all of which work to inhibit BDNF(119).

A variation known as the rs4074134 SNP changes the codon value of the BDNF gene from A to G in an intron at position 27625738, which is 31 kb upstream of the 3' region. According to reports, the frequencies of minor alleles range from 0.11 to 0.56 in different ancestral groups(29). Although scientific proof is still lacking, empirical evidence relating the mutation to multiple behavioural traits lends credence to the idea that its location within an intron can affect gene expression via gene splicing. The SNP rs4074134 has been previously linked to alterations in addictive behaviours associated with tobacco consumption and obesity. No phenotypes have been identified that correspond with this polymorphism in relation to neurodegenerative illnesses; nevertheless, it has been claimed to be associated with long-term memory. Furthermore, if the BDNF-AS gene modulates BDNF expression, exploring interventions in the progression of cognitive and neurodegenerative illnesses merits thorough investigation(120).

The G-712A polymorphism has recently been found to be associated with substance use; it is located in the presumed promoter region of the BDNF gene, 712 base pairs upstream of the initial exon. Computational investigation revealed in one study that this region's sequence might be part of the binding site for eukaryotic polymerase II promoters; furthermore, the polymorphism could disrupt the recognition pattern, which could have a negative effect on BDNF gene transcription(121). Only a single study has demonstrated a robust correlation between the G-712A genotype distribution and Major Depression. Individuals possessing this polymorphism exhibit heightened vulnerability to disease onset. These results underscore the significant involvement of the G-712A polymorphism of BDNF in major depression

and may inform future research aimed at uncovering genetic risk factors for this condition; yet, no studies have yet explored the association of this polymorphism with neurodegenerative or metabolic disorders(122).

The rs2049045 polymorphism is an intronic variant located between exon 2 and exon 3 of the BDNF gene. This “single nucleotide polymorphism (SNP)” replaces a G with a C and has an average minor allele frequency of 0.06, ranging from 0.19 in individuals from Europe to 0 in those from East Asia. This SNP exhibits significant “linkage disequilibrium (LD)” with the rs6265 polymorphism. Reports indicate that these genetic variants in BDNF significantly influence susceptibility to depression associated with AD(123).

They may serve as effective prognostic indicators of AD in the future. Other research has examined BDNF haplotypes, including rs2049045, and their association with PD risk. This study was a case-control analysis conducted in three different Caucasian cohorts of PD, utilising eight tagged single nucleotide polymorphisms and five created haplotypes. Throughout all of the studies, there was not a significant variation in the genotype and allele frequencies between the control group and the patients. Since BDNF polymorphisms are so close together and may serve as an early disease marker, it is crucial to study them as haplotypes(124).

Chromosome 11, in the 5' noncoding region of the BDNF gene, contains the rs2030324 polymorphism, often known as C270T, at position 27,705,368 on the forward strand. A 2.2% increase in AD risk was associated with the BDNF 270T variation. Approximately four years is subtracted from the Late Onset age by the BDNF TT genotype. Additionally, an increased risk of developing Alzheimer's disease-related depression was associated with a haplotype that included the G11757C, G196A, rs2049045 C/G, and C270T loci(29).

A study indicates a correlation between the existence of the T allele and the incidence of familial Parkinson's disease. It appears from the data that there may be a genetic imbalance between the C270T variant and a mutation in the BDNF gene's coding region, suggesting that this gene could have a role in the onset of Parkinson's disease in families. People who carry this polymorphism on the T side are more likely to suffer from “post-

traumatic stress disorder (PTSD)” and other neurological disorders(125).

6. BDNF- Targeted Gene Therapy: Therapeutic Strategies and Preclinical Evidence

Comprehending the potential of BDNF gene therapy in addressing AD requires a comprehensive analysis of its basic underpinnings. The implementation of BDNF gene therapy encompasses complex biochemical pathways aimed at improving synaptic function and neurogenesis, therefore mitigating the cognitive loss associated with AD.

BDNF facilitates synaptic plasticity via many chemical processes, creating a milieu that supports neuronal growth and resilience. Identifying specific pathways, including those related to pro-inflammatory indicators and protein inhibitors like PAI-1, is essential for maximising the efficiency of BDNF. The translation of molecular discoveries from BDNF gene therapy into therapeutic applications is anticipated to provide several benefits(126).

Gene therapy may alleviate the cognitive and behavioural abnormalities shown in AD patients by potentially elevating the brain's BDNF levels. This method is supported by preclinical research that has demonstrated significant enhancements in cognitive function and a reduction in disease in animal models(127).

These are encouraging results, but combination therapy and new drug carriers are needed to make combination therapy more effective due to the complexity of Alzheimer's pathology. The goal of BDNF gene therapy is to boost BDNF in the brain, and this could not only slow the loss of cognitive function associated with Alzheimer's, but perhaps reverse it. This involves intricate biochemical pathways that play key roles in regulating synaptic plasticity and promoting neurogenesis. BDNF enhances the activity of synapses, creating a stronger "neuronal environment" that is conducive to learning and memory(128).

The clinical effects of Alzheimer's on clinical parameters such as A β pathology are expected to be significantly affected by the increase in BDNF levels. Exogenous administration of BDNF has been shown to have beneficial effects on cognitive and behavioural deficits, and to reduce A β pathology in mice models, providing strong evidence for the beneficial role of BDNF gene therapy(84). The precise biological processes by which BDNF gene therapy is believed to work have

been a focus of much research, including the protein inhibitors, including “Plasminogen activator inhibitor-1 (PAI-1)”, which are known to block the maturation of BDNF(107).

The current research has shown that PAI-1 and the subsequent delayed BDNF maturation could be a key mechanistic pathway that is affected by environmental factors, according to studies (Gerenu et al., 2017, p. 10). These findings highlight the intricate interaction between genetic and environmental factors in assessing the effectiveness of BDNF as a therapeutic target(129). Genetic treatments to specifically target these molecular pathways could lead to enhanced BDNF production and activity, resulting in greater neuroprotection against AD-related neurodegeneration. The anticipated response to the elevation of BDNF via gene therapy points to its therapeutic potential and illuminates the broader clinical implications for individuals with AD. The cognitive improvement and behavioural outcome changes that are proposed are compatible with current preclinical data, and thus suggest potential clinical utility(130).

Although preliminary animal model trials have yielded encouraging outcomes, the intricacy and variability of AD necessitate a holistic strategy, possibly using combination medications or novel delivery mechanisms to enhance therapeutic effectiveness. This paradigm shift towards gene therapy may extend beyond Alzheimer’s, offering insights into therapeutic strategies for other neurodegenerative illnesses. Ongoing study and enhancement of BDNF gene therapy methodologies promise to usher in a new age in the treatment of cognitive decline and neurological wellness, signifying a substantial advancement in our scientific and clinical comprehension of neurodegeneration(131).

7. Gene Delivery Systems and Emerging Technologies

7.1 Use of viral and non-viral vectors for targeted gene delivery.

While initial studies with animal models have shown promising results, the complexity and heterogeneity of AD require a comprehensive approach, which may involve the use of combination drugs or novel drug delivery systems to improve therapeutic efficacy. Such a change in paradigm may have implications for other neurodegenerative diseases, as well as Alzheimer’s. The continuous research and improvement of

BDNF gene therapy techniques hold the potential to usher in a new dawn in the field of cognitive decline and neurological well-being, representing a significant leap in both scientific and clinical understanding of neurodegeneration(132).

Exploring new methods of delivery will be an important aspect of improving BDNF gene therapy for AD to overcome the critical challenge of delivering therapeutic molecules efficiently across the BBB. These systems are designed for more precise targeting and increased bioavailability of BDNF and thus optimize its therapeutic efficacy in the fields of neurodegeneration. These new delivery systems aim to overcome the formidable obstacle of the brain’s immune response system to provide therapeutic levels of BDNF to the target neurons in order to optimize synaptic plasticity and cognition(133).

Furthermore, in order to get around these obstacles and enable long-term, regulated BDNF activation, novel methods including viral vectors and nanoparticle-mediated delivery have recently been introduced. By altering the delivery method and biological utility of BDNF gene therapy for AD, these tactics may allow for improved clinical efficacy. There are two main delivery systems: a) Delivery by viral vectors. Viral vectors have been engineered as highly efficient tools for gene delivery, due to their ability to transduce many cell types and to provide stable and long-term expression of therapeutic genes. “Adeno-associated viruses (AAVs)” are especially promising for BDNF delivery because they are non-pathogenic, capable of carrying large DNA inserts, and elicit minimal immune responses(134).

AAV vectors have successfully delivered BDNF genes to neurons, with substantial neuroprotective effects and improved functional recovery in multiple preclinical models of dementia. Hence, precise control of the timing and duration of BDNF expression through promoter elements in these viral vectors is important. The use of tissue specific promoters allows for targeted delivery to certain brain regions therefore reducing the risk of adverse effects associated with widespread expression. In addition, inducible expression systems, which enable the activation of the therapeutic gene in response to specific stimuli, are one of the possibilities for precise regulation of BDNF levels in the brain(135).

Mode I	Vector	Delivery methods	Key findin	Refer ences
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			gs	
APP transgenic mice	AAV2-BDNF	Direct injection into the entorhinal cortex	Restored synaptic function and improved learning and memory without affecting amyloid plaque load	(136)
Nonhuman primates	AAV2-BDNF	MRI-guided injection into the entorhinal cortex	Elevated BDNF protein levels in neurons; no significant safety issues observed	(137)
Nonhuman primates	AAV2-BDNF	MRI-guided injection into the entorhinal cortex	Increased FDG-PET signal in treated regions; no significant adverse events reported up to 15	(136)

			months post-treatment	
AppNL-G-F mice	Encapsulated cell bio-delivery (ECB) device releasing BDNF	Bilateral hippocampal implantation	Improved spontaneous behavioral alterations in the Y-maze test; well-tolerated with no significant side effects	(138)
APP/PS1 transgenic mice	AAV-BDNF with ADTC5 (BBB modulator)	Intracerebroventricular injection	Enhanced cognitive performance; increased synaptic plasticity markers; no effect on amyloid plaque load	(139)

Table: Summarises preclinical evidence where AAV-2 mediated BDNF delivery shows improved neuronal function and metabolic activity with no significant adverse effects.

b) Nanoparticle-mediated delivery: Nanoparticles are a new method for the delivery of BDNF that increases the solubility and stability of the therapeutic protein and helps it pass through the BBB. Polymeric nanoparticles, gold nanoparticles

and Liposomes, are among the various types of nanoparticles that have been studied for their capacity to encapsulate and deliver BDNF. For example, surfactant-coated nanoparticles have demonstrated the ability to transport BDNF across the BBB via receptor-mediated exocytosis, thereby ensuring therapeutic levels of BDNF reach neuronal targets(140).

The advantage of using nanoparticles is their tunable properties. Size, surface charge and hydrophilicity can be altered to improve delivery efficiency and cellular uptake. Moreover, nanoparticles can be engineered to provide controlled release of BDNF for extended durations, crucial for sustained therapeutic levels in the CNS, eliminating the need for repeated injections. The inclusion of regulatory elements in the design of delivery systems is essential to obtain controlled and accurate expression of BDNF(141).

Endogenous pathways controlling neuronal activity and calcium signalling can be used to synchronise BDNF release to the physiological state of the tissue. Exploiting the Ca^{2+} influx during synaptic activity to enhance the localised release of BDNF can fine-tune therapeutic effects at the required site(142). Furthermore, small compounds that modulate transcription factors associated with BDNF expression could be administered together with the main therapeutic drugs, providing another level of regulation. Pharmacological drugs that activate the “cAMP response element-binding protein (CREB)” signalling pathway may increase BDNF transcription in target neurones, thus having a combinatorial effect to enhance neuronal survival and functionality(143).

A recent study published in PNAS showed that AAV9 delivery of human wild-type Presenilin-1 (hPS1) can significantly ameliorate many AD-related impairments in PSEN mutant mice. These animals carry mutations in the PSEN1 gene, which disrupt the activity of γ -secretase and cause the accumulation of APP fragments and the progression of neurodegeneration.

The researchers administered the AAV9-hPS1 systemically, leading to widespread expression across the brain. The gene therapy approach restored γ -secretase activity as evidenced by the marked decrease in APP C-terminal fragments(144). It also improved memory deficit as treated mice showed improved performance in spatial learning and memory evaluations such as the Morris water maze. In addition, deficits in

synaptic plasticity were rescued and hippocampal long-term potentiation restored. AAV9-hPS1 administration significantly ameliorated neurodegeneration, protecting cortical neurones and reducing markers of gliosis such as activated astrocytes and microglia. These findings support the therapeutic utility of AAV9-mediated delivery of functional PSEN1 in the context of PSEN1 mutations that cause early-onset AD, representing a major advance in gene therapy for familial forms of the disease(144)(145).

The preclinical findings endorse the viability of employing AAV9 vectors for gene therapy aimed at PSEN1 mutations in AD. The potential restoration of γ -secretase activity and mitigation of neurodegeneration offer opportunities for the development of therapeutic strategies for patients with early-onset AD due to PSEN1 mutations. Further clinical studies are required to assess the safety, effectiveness, and enduring advantages of this therapy in humans.

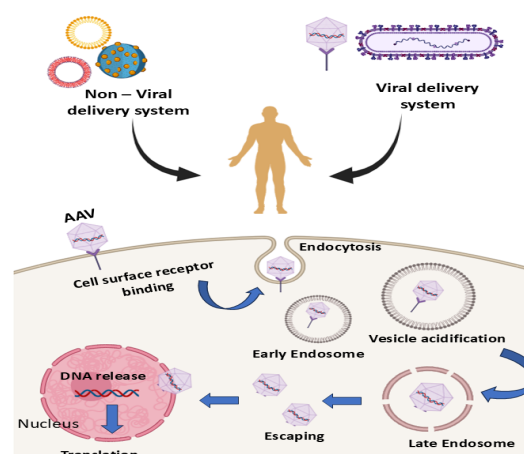


Figure 4: Illustrating the general idea behind AAV-based gene therapy's potential as a treatment for dementia

8. Challenges and Future Directions

BDNF gene therapy for AD is limited by multiple biological and technical hurdles. The biggest hurdle is the complex mechanisms that regulate and modulate BDNF growth in the brain. BDNF maturation is essential for its activity and tightly controlled by molecular mechanisms(146). The development of BDNF depends on plasmin and is tightly regulated by “Plasminogen activator inhibitor-1 (PAI-1)”, which is of critical importance in the brain (Gerenu *et al.*, 2017)(129). Any disruption or deficiency of this regulation

could affect the availability and activity of BDNF, which is a major challenge in the development of gene therapy regimens to alleviate the symptoms of AD. In addition, the role of PAI-1 in the regulation of BDNF maturation involves not only biological processes but also environmental factors, thus adding further complexity to therapeutic applications(147).

In addition, technical challenges of BDNF gene therapy, including effective delivery mechanisms and accurate regulation of BDNF expression levels, should be addressed. Effective delivery techniques are essential to ensure delivery of the BDNF gene to the targeted areas of the brain affected by Alzheimer's disease without adverse effects or immune responses. Methods for improving the accuracy and safety of gene delivery systems, including viral vector-based and nanoparticle-based systems, are being explored. The expression of BDNF should be finely tuned to prevent overexpression that could lead to unwanted physiological effects. Overcoming these biological and technical hurdles will allow future clinical applications in the fight against Alzheimer's disease and enable the building of a robust and successful BDNF gene therapy paradigm to alleviate cognitive deterioration while meeting safety criteria.

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