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Advancements in Alzheimer's Treatment Using Gene Therapy Techniques.

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Abstract

Background

Alzheimer's is a neurodegenerative disorder of brain and a very common form of dementia. Due to damage to the cortical and subcortical areas of brain there is disturbance of multiple functions like memory, thinking, judgement and orientation. Alzheimer disease is an irreversible progressive disorder which is caused by the formation of the neurofibrillary tangles of tau proteins and amyloid-ß plaques. The excessive deposition of β-amyloid peptides and intracellular neurofibrillary tangles of tau protein cause damage to the DNA and RNA. One of the clearly identified genetic factors involved in the Alzheimer disease is Apo lipoprotein E. Mutations in amyloid precursor protein, presenilin 1, and presenilin 2 genes have also been identified and are associated with the onset of the early-onset familial Alzheimer disease. AD can be Sporadic AD and Familial AD. There are many other factors that increase the risk for AD, which include family history, hypertension, sleep disorders, obesity, and oxidative stress.

Objective

This article is a review of role of genes in the Alzheimer's disease along with the various approaches for the AD treatment by gene therapy.

Method

Numerous research articles and review articles were searched on various related journals using keywords like "Genetics in Alzheimer's", "Neuro-degenerative disorder", "Genetic biomarkers", "Dementia".

Conclusion

This review is concluded by giving various hypotheses for using genetics in the treatment for Alzheimer's disease.

Keywords: Alzheimer's disease; Gene Therapy; Brain Disorder; Neurodegeneration, CRISPR/Cas9; Amyloid Plaques; Tau

Introduction

Neurodegenerative disorders include a large spectrum of diseases which affects the various activities of daily life and reasoning of a person. Human brain is a very unusual and complex organ which comprises of various cell types including neurons, astrocytes, oligodendrocytes, tanycytes, microglia, and blood vessels.[1] Because of the complexity of human brain, the mechanism and treatment of various neurodegenerative disorders is still not developed[2] and thus, the current treatment majorly involves the prevention of the further prognosis of such diseases.

Alzheimer's Disease is a type of neurodegenerative disorder and the most common form of Dementia.[3] Dementia is expected to affect 66 million people globally by 2030.[4] Alzheimer's disease (AD) is a permanent, irreversible neurological disorder marked by memory loss, thinking and reasoning impairment, and personality and behavioural changes. The first signature case and the pathological features of the disease were identified by Alois Alzheimer in 1906. Emil Kraepelin, one of his co-workers, later named the disease after him in 1910.[5]

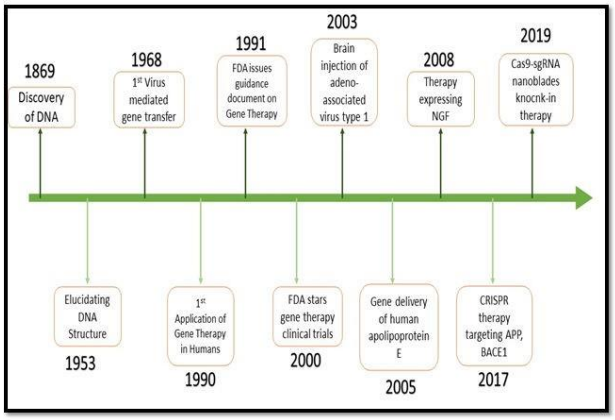

Figure1: Timeline of historical aspects of gene therapy [insert figure 1]

Based on theories devised by Edward Tatum in 1966, the early concept of viral gene transfer mediated therapy was proposed by Rogers group. The same group later pioneered the first trial based on gene therapy.[6] Marshall Nirenberg, a renowned Nobel laureate initiated a dialogue on gene therapy through his

paper on "synthetic messages".[7] The first genetic transfer experiment done in 1989 was approved by the then director of the National Institute of Health, James Wyngaarden. Due to the immense success in relevant gene therapies, there were consequent European approvals of various gene therapy products.[8] In 2016, Unites States Food and Drug Administration provided accelerated approvals for many products.[9] These provided a thrust for researchers to engage in development of gene therapy.[7] In 1980s, the genetic material of Escherichia coli was identified. Clustered Regularly Interspaced Short Palindromic Repeats and Associated proteins were recognised as extra-chromosomal in 2005. These tools were considered as a promising biotechnology aid.[10] Glybera, a gene-based product made by Amsterdam Molecular Therapeutics got approval by European Medicines Agency. This adeno-viral associated vector product was developed for treatment of lipoprotein lipase deficiency. This approval marked a promising thrust in the era of gene therapy throughout the globe.[**6**] There have been considerable advancements in the field of gene therapy from 1989 till 2012. Presently, gene therapy is considered a promising approach for targeting many diseases. More number of manufacturing companies are initiating to invest in this arena of therapeutics and consequently, more products are undergoing clinical trials.[11] In 2005, phase I clinical trial results showed improved cognition and better morphological function of cholinergic neurons mediated by autologous fibroblasts of the NGF delivered by recombinant vectors. It was concluded that this therapy could pave a promising way for future therapeutics.[12] In 2014, the first ever phase1/2 open label dose escalation study trial of a lentiviral vector encoding aromatic amino acid decarboxylase was conducted with the aim of maintaining a continuous dopamine supply in the motor region.[13] At the G8 dementia summit organised in 2013, an emphasis was laid on the need for gene-based therapies and better treatments for Alzheimer's due to the escalation in cost expenditure by the society in tackling this disease.[14]

Aside from age, which is the most obvious risk factor for the disorder, epidemiological reports have pointed to a number of possible links like head injury, reduced brain size, low educational and occupational attainment, low mental ability, and reduced mental and physical activity during late life. The cholinergic hypothesis, the amyloid hypothesis, the tau proliferation hypothesis, the mitochondrial cascade hypothesis, the calcium homeostasis hypothesis, the inflammatory hypothesis, the neurovascular hypothesis, the metal ion hypothesis, and the lymphatic system hypothesis are some of the theories that have been proposed, are descriptive hypothesis about the triggers of AD.[5] Both varieties of Alzheimer's i.e. Early-onset and late-onset have defining genetic components. Early-onset of Alzheimer's is shown to possess causal mutations in 3 genes, defining the elemental role of amyloid in the disease, that has been the most extensively researched mechanism since these findings.[4]

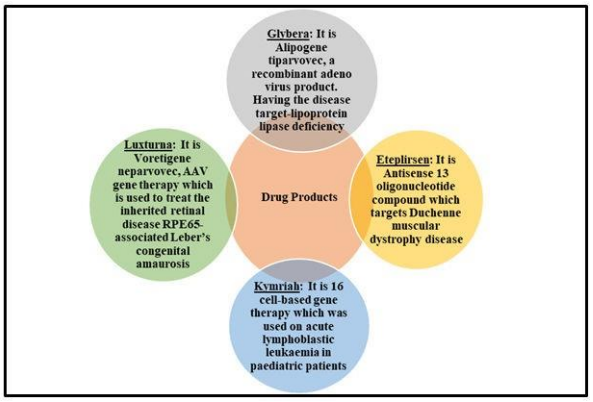

Figure2: Early drug product approvals in history of gene therapy [insert figure 2]

Development and Causes

AD is the most common cause of dementia. In the 65–69-year age group[15], the incidence of AD rises from 2.8 per 1000 person years and 56.1 per 1000 person years in the age group of older than 90 year's age. About 10 percent of people older than 70 have substantial memory loss, and more than half of these people have AD. Among people older than 85 years, an estimated 25-45 percent have dementia.[16]

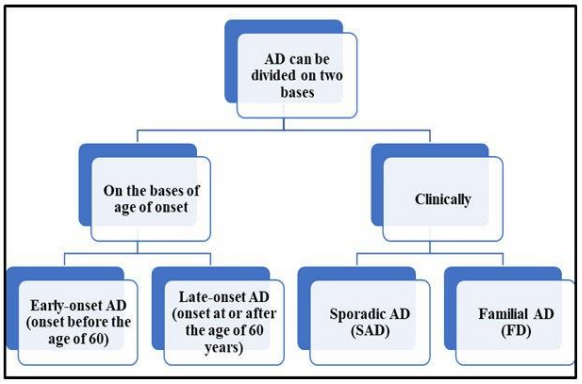

Figure3: Classification of AD [insert figure 3]

Late- onset AD occurs in most patients with AD (>95%), whereas EOAD accounts for a small proportion of these patients (<5%). Difference between these 2 types has never been clear, and cases that sometimes span these age groups remain a puzzle.[16, 17]

FD accounts for 1–5% of all AD cases. The genetic factors that are currently believed to be responsible for Familial AD are APP (Amyloid Precursor Protein), PSEN 1 (presenilin 1) and PSEN 2 (presenilin 2); whereas APOE is believed to be responsible for SAD.[5, 17]

Clinical Features

Neurodegeneration starts 20-30 years before the clinical onset. Plaques and tangles are present in the brains of AD.[18] So, Plaques and tangles increase after certain threshold. The

initial clinical phase is Mild Cognitive Impairment[15]. Plaques, tangles and cholinergic deficits are more severe in Early onset AD. In young patients, there is a correlation between the severity of disease and the plaques and tangle burden while such correlation is not associated with elderly patients; based on plaque and tangle load, it may be difficult to distinguish elderly patients with Alzheimer's disease from non-demented individuals of the same age. Neuronal death occurs in Alzheimer's disease which can be co-related with the changes like acetylcholine deficiency, glutamate excitotoxicity, deposition of Amyloid β plaques, formation of neurofibrillary tangles of phosphorylated tau protein, and the overall neuronal loss. Impairment of episodic memory, aphasia, agnosia and general cognitive symptoms like orientation, decision making and judgement is affected in AD.

Causes of Alzheimer's

It is presumed that there is extended time lapse between exposure and onset of disease. The progression of AD occurs over 1-3 decades, and the average time between events and disease onset varies from several years to several decades, making it difficult to distinguish individual factors that are responsible for the onset.[19] Various causes can contribute to the aetiology of AD which can include but are not limited to factors like genetics, ageing, injury, environmental factors, certain chemicals etc. The LEARn (Latent Early–life Associated Regulation) model with an underlying "two-hit" hypothesis was suggested, which combines factors of genetic and environmental risk in an Epigenetic path.[19]

Environmental Causes

The role of environmental exposures and their mechanisms contributing to the pathogenesis of AD is still not very well understood. This is assumed to be due to the potentially long time-interval between exposure and the emergence of the disease.[20] Due to long term exposure of the environmental contaminants (see Figure 4) over the years of individuals life, its speculated that such contaminants may induce neuroinflammation which may be regarded as a feature paving the way towards the development of AD. Environmental chemicals of various classes have been hypothesized to play role in development of AD. There are number of literatures present which identify both organic and inorganic chemicals as possible risk factors for the development of AD.[19]

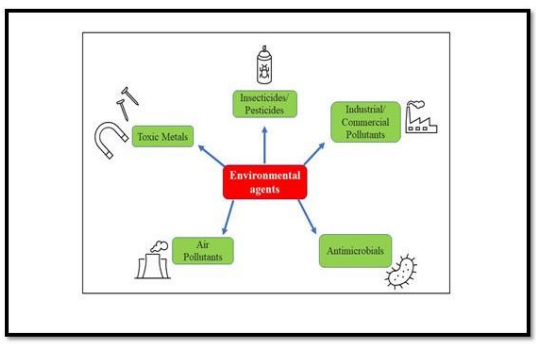

Figure4: Various Environmental agents speculated to cause AD. [insert figure 4]

Genetic Causes

Genes involved in Familial AD

FD is an Autosomal dominant disorder. Common characteristic of Familial AD is that its onset is before 65 years.[16] Majorly, APP is involved in the Familial AD. The human APP gene was first identified to describe the corresponding cDNA in 1987 using partial protein sequence information from purified β-amyloid (Aβ).[23, 24] The first mutation was identified in Amyloid Precursor Protein (APP) gene on chromosome 21 and then several additional mutations were also found on APP. But only few cases can be explained by APP mutations.[23, 25] Apart from the mutations in APP, rare and fully penetrating mutations in presenilin-1 (PSEN1) on chromosome 14, and presenilin-2 (PSEN2) on chromosome 1 cause early-onset FD, comprising <1% of AD cases (see Table 2).[26]

Genes involved in Sporadic AD

In case of SAD, there is reported association of Apolipoprotein (ApoE) ε4 allele. ApoE ε4 allele acts by modifying the age of onset for AD.[27] ApoE basically acts as cholesterol transporter in the brain[28, 29]. ApoE has three isoforms: ApoE ε2 (Cys112, Cys158), ApoE ε3 (Cys112, Arg158), and ApoE ε4 (Arg112, Arg158).[30] ε4 allele is less efficient than the other variants in the reuse of membrane lipids and neuronal repair.

Additionally, single nucleotide polymorphisms in or around CR1, PICALM, and BIN1 have been shown to have genome-wide interaction and replication; these were the genes discovered in the first wave of massive, collaborative genome-wide association studies. The association with single nucleotide polymorphisms in MS4A cluster, CD2AP, CD33, EPHA1, and ABCA7 was discovered by collective efforts (see table 1).[2, 31]

Table1: Various causal and risk genes in AD. [Insert table 1]

Genes	Chromosome	Location of mutations or main SNP	Inheritance pattern	Proposed function	Implicated pathway
APP	19	Exons 16 and 17	Autosomal dominant or recessive	Cell signalling, amyloid ß peptide substrate, phosphorylation of tau, activation of GSK 3ß	Amyloid β pathway, endocytotic receptor trafficking, tau pathway
PSEN 2	2	Whole Gene	Autosomal dominant	γ-secretase activity, transmembrane protein processin	Amyloid β pathway, synaptic plasticity, neuronal survival

				g, intracellular signalling	
APOE	19	Exon 4	Semi-dominant	ß-Amyloid aggregation and clearance, intracellular signalling through LRP	Lipid transport and metabolism, amyloid β pathway, synaptic plasticity, neuroinflammation
CLU	8	Intronic rs1136000	Risk gene	Molecular chaperone, synapse turnover, amyloid β aggregation, clearance, and toxicity	Amyloid β pathway, lipid metabolism, immune system, inflammation, apoptosis
CR1	1	Intronic rs6656401	Risk gene	Complement system activation, amyloid β clearance	Immune system, amyloid β pathway
PICALM	11	Upstream rs3851179	Risk gene	Clathrin-mediated endocytosis	Synaptic cell functioning, amyloid β toxic effects, processing of APP
MS4A4A, MS4A6E	11	Intergenic rs610932	Risk gene	No known functions (except MS4A2 β-subunit, which has high affinity for IgE receptors)	Immune system (MS4A2), cell surface signalling
CD33	19	Upstream rs3865444	Risk gene	Clathrin-mediated endocytosis	Immune system, synaptic cell functioning
BIN1	2	Upstream rs744373	Risk gene	Synaptic vesicle endocytosis, formation of tubular membrane	Synaptic cell functioning, caspase-independent apoptosis
EPHA1	7	Upstream	Risk gene	Synaptic develop	Immune system
		rs11767557		ment and plasticity	
ABCA7	19	Intronic rs3764650	Risk gene	Transportation of substrates across cell membranes	Cholesterol metabolism, immune system, processing of APP

Currently employed treatments for alzheimer's

There are no drug therapies currently that provide a complete cure for AD. Various therapies and combination therapies have been developed (see table 2) that may improve symptoms or slow down the neuropathology. The main types of drugs and drug combinations used to treat AD patients are cholinesterase inhibitors and NMDA receptor antagonists. According to clinicaltrials.gov as of 2020, there are 121 different treatments in clinical trials for Alzheimer's disease (AD) (see table 3).[32] The majority of medications in the Alzheimer's disease pipeline are presumed disease-modifying agents that aim to slow or stop the development of the disease.[32]

Aducanumab (Aduhelm): It is a Monoclonal antibody which got a very recent FDA approval for AD treatment under the "Accelerated approval pathway" in June 2021.

Table2: Drugs prescribed for AD treatment. [insert table 2]

DRUG	CHEMICAL CLASS	ACTION	ROUTE OF ADMINISTRATION	TIME OF APPROVAL (FDA)	CURRENT STATUS
Tacrine	Alkaline	AChE inhibitor	Oral or rectal	1995	Withdraw
Donepezil	Piperidine	AChE inhibitor	Oral	1996	Approved
Rivastigmine	Carbamate ester	AChE and BChE inhibitor	Oral or transdermal patch	1997	Approved
Galantamine	Phenanthrene Alkaloid	AChE inhibitor	Oral	2001	Approved
Mementine	Glutamatergic Modulator	NMDA antagonist	Oral	2003	Approved
Memantine/ Donepezil fixed-dose combination	Glutamatergic modulator/ Piperidine	NMDA antagonist/ AChE inhibitors	Oral	2014	Approved

Table3: Current status of selected drugs in clinical trials. (https:// clinicaltrials.gov) [insert table 3]

Drug	NCT number	Study Start Date	Current status	Sponsor	Mechanism of Action	Route of admini

	(https://clinicaltrials.gov)					stration
AADvac1	NCT02579252	2016	Phase 2	Axon Neuroscience SE	Tau vaccine	Active vaccine
ANAVEX2-73 (blarcamesine)	NCT03774459	2018	Phase 2 (completed)	Anavex Life Sciences Corp.	Sigma-1 receptor agonist, M2 auto-receptor antagonist	High dose ANAVEX2-73: Active oral capsule Mid dose ANAVEX2-73: Active oral capsule
ALZT-OP1	NCT02547818	2015	Phase 3	AZ Therapies, Inc	inhibits aggregation of Aβ	Active capsules
AVP-786	NCT03393520	2017	Phase 3 (Recruiting)	Avanir Pharmaceuticals	Weak antagonist of NMDA receptors, and an agonist of sigma 1 receptors	Oral capsules
BAN2401 (Lecanemab)	NCT03887455	2019	Phase 3 (Recruiting)	Eisai Inc.	Humanized IgG1 version of mAb158 binds to large, soluble Aβ protofibrils	I.V. infusion
CAD106	NCT01097096	2010	Phase 2	Novartis Pharmaceuticals	Aβ vaccine	Intramuscular injections
Elenbecestat	NCT02956486	2016	Phase 3 (terminated)	Eisai	β-secretase enzyme inhibitor	Oral tablet
Gantenerumab (RO4909832)	NCT03444870	2018	Phase 3	Roche/Genentech	Aβ-specific mAb	SC injections
LMTM (TRx0237)	NCT03446001	2018	Phase 3	TauRx Therapeutics	tau protein aggreg	Oral tablets
					ation inhibitor	
Solanezumab (LY2062430)	NCT02760602	2016	Phase 3 (terminated)	Eli Lilly	Aβ-specific mAb	Administered IV

*For more drugs in clinical trials visit https:// clinicaltrials.gov

Various approaches for the ad treatment using gene therapy

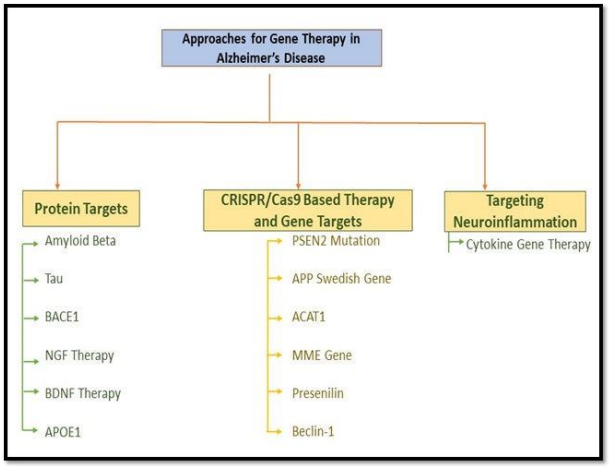

Figure6: Various approaches for the AD treatment by gene therapy. [insert figure 6]

Protein targets

Amyloid beta plaques are a common occurrence in Alzheimer's disease. Consequently, many strategies have been attempted to target these plaques. *Another study done by Carty et al. was performed which targeted the expression of endothelin converting enzyme (ECE) through adeno associated virus 5 intracranially administered. It was observed that upregulated ECE led to reduced amyloid body deposition.*[1]

Aducanumab (Aduhelm): It is a Monoclonal antibody which acts by forming complex with Amyloid- beta and thus the deposition of plaques gets hindered. If its effectiveness gets proven then it can become one of the first medication that targets Amyloid body deposition.

A tau knockout strain mediated genomic edit on introns and exons in the MAPT gene was experimented by Tan et al. The preclinical studies performed in young mice resulted in reduction in excitotic seizure activity. [1]

Beclin 1 is a macromolecule which is concerned in the regulation of autophagy and has been shown to be reduced in Alzheimer's disease patients. Beclin 1 deficit cured through lentiviral mediated overexpression is a potential therapy that improves autophagy by facilitating revival of Beclin 1.[1]

NGF (nerve growth factor) is an endogenous neurotrophic factor which regulates the growth and survival of cholinergic

neurons in the basal forebrain via functional TrkA receptor activation. [33, 34] Tuszynski et al. performed ex vivo NGF gene transmission in eight people with moderate Alzheimer's disease was studied in a phase I experiment, which involved implanting autologous fibroblasts genetically engineered to express human NGF into the forebrain.[33] Bishop et al. examined the therapeutic potential of AAV2-NGF (CERE-110) in rodent basal forebrain cholinergic neurons for targeted, stable, and sustained NGF transmission and trophic activity. Their findings show that NGF transgene delivery to the intended brain region is safe, precise, and results in long-term NGF expression with no protein loss or accumulation.[35]

Brain derived neurotrophic factor (BNDF) influenced the sustenance of entorhinal cortex and neurons of the hippocampus in many animal models in Alzheimer's. This effect occurred independent of the alterations seen in amyloid beta.[1]

It has recently been suggested that excess ApoE4 could lower the Brain Derived Neurotropic Problem (BDNF) expression inside the hippocampus of AD patients owing to enhanced nuclear translocation of Histone Deacetylaseses (HDACs).[28, 36] An adeno viral vector with genetic codons for human BDNF when given through the intralateral ventricular route was successful in stabilising the expression of BDNF as well as the restoration of BDNF amount in the brain. Enhancing the BDNF levels through this therapy reduced the behaviour associated side effects and reduced loss of neurons and alleviation of synaptic degradation was also observed.[37]

CRISPR/Cas9

Presenilin autosomal mutation was corrected by use of CIRSPR/Cas9 in iPSC-derived neurons. The N141I mutation was corrected which normalised the amyloid beta ratio. APOE's rarest allele E2 enhances risk of Alzheimer's disease by 40%. Using CRISPR/Cas9 for conversion of APOE4 to APOE2 or APOE3 prevents the pathogenesis of APOE4 associated Alzheimer's progression.[38]

Mutation in APPswe is another promising target. Adeno associated viral CRISPR/Cas9 delivery showed about 2% of indel formed in the mutated allele. A target locus present in only 2 copies in the genome, even higher indel was formed which substantiated a proof for this approach.[39, 40] Adeno associated viral delivery of miRNA leading to knockdown of 1 reduced ab in a mouse model of Alzheimer's disease. Intracardiac delivery of neprilysin through an adeno viral 9 vector reduced amyloid beta levels as well as enhancement in memory. Leptin gene delivered through a lentiviral vector was injected into double transgenic mice which reduce tau phosphorylation and improve density in the synapse. [41]CRISPR-Cas9 is a promising technology which facilitates creation of genetic tools for correction of unwanted mutations present in genes responsible for pathology of Alzheimer's namely PSEN1, PSEN2 and APP.[42] In vivo genetic manipulations of the post-mitotic neuron in the adult brain are a plausible target for gene therapy. CRISPR-Cas9 based nanocomplex when given to adult mice brain showed very less off-target associations. This therapy was designed to target the BACE1 associated suppression of amyloid beta.[43] Neprilysin also called as the membrane metalloendopeptidase enzyme is a causative factor for Alzheimer's. It degrades amyloid beta and variations in the associated gene for neprilysin is considered an important factor for pathology of Alzheimer's.[44]

Targeting Neuroinflammation

A novel gene therapy constituting adeno-associated virus containing an artificially made microRNA targeted CD33. This therapy was able to reduce Aβ40 and Aβ42 levels both after 2 and 8 months respectively. This adeno-viral therapy based on knockdown of CD33 was responsible for reduction of amyloid beta as well as neuroinflammation of the brain.[45] The neuroinflammation is mediated by the cerebral immunogenic cells. It is a plausible targeted due to promise shown in both pre-clinical and clinical studies. The causes of such pathology are neurodegeneration, heat shock proteins, tau etc. These attach to associated receptors and cause induction of signalling pathway that causes inflammation through various inflammatory mediators which can even lead to cell death.[46, 47]

Conclusion

Currently for the treatment of AD there are four drugs and one combination therapy which are clinically prescribed, this limits the options for treatment of such a complicated disease. Developing Gene therapy in the AD treatment will provide another option or it can also be developed as an early diagnostic tool for the disease hence preventing the neuronal loss at early stages. The four Alzheimer's disease genes discovered in the 1990s- APP, APOE, presenilin 1, and presenilin 2 provided crucial insight on the disease's pathogenesis at the molecular level. Before the large-scale GWAS, very little progress was made in the identification of the genes involved in the AD, but after the large scale GWAS organised by European and international genome-wide association collaborations nine novel risk loci were uncovered. But APOE still remains the most significant gene for complex Alzheimer's disease, with a lifetime chance of 35 percent. This article draws attention to the function of genes in Alzheimer's disease, as well as the multiple gene therapy approaches for treating the disease. Overall, we believe that considering and developing gene therapy-based treatments will accelerate progress for people at risk with or dealing with Alzheimer's disease.

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