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Mini Review

The Genetic Puzzle of Alzheimer's: Pathways, Controversies, and Future Directions

Shanghua Fan[1#], Lijun Deng[1#] and Hongjuan Dong[2*]

[1]*Department of Neurology, Sixth Hospital of Wuhan, Affiliated Hospital of Jianghan University, China.*

[2]*Department of Neurology, Renmin Hospital of Wuhan University, China.*

[#]*Contributed equally.*

***Corresponding author**

Hongjuan Dong, Department of Neurology, Sixth Hospital of Wuhan, Affiliated Hospital of Jianghan University, Wuhan, 430014, China.

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Abstract

This review focuses on the genetic basis, epidemiology, pathophysiological mechanisms, diagnostic advances, therapeutic strategies, and controversies in Alzheimer's disease. It synthesizes findings from numerous studies to provide a detailed understanding of the disease. The genetic factors, including key genes and risk factors, play crucial roles in Alzheimer's disease. Epidemiological studies explore the prevalence and genetic influences in different populations. Pathophysiological mechanisms involve amyloid precursor protein, tau protein, and neuroinflammation. Diagnostic advances aim to identify genetic biomarkers and improve genetic testing. Therapeutic strategies include gene therapy, pharmacogenomics, and emerging genetic therapies. Controversies and future directions cover ethical issues, the role of genetics versus environment, and potential research areas. Overall, this review offers insights into the complex nature of Alzheimer's disease and potential avenues for future research and treatment.

GENETIC BASIS OF ALZHEIMER'S DISEASE

Historical perspectives on Alzheimer's disease genetics

Alzheimer's disease (AD) genetics has a rich historical backdrop. The discovery of the Apolipoprotein E ε4 (ApoE ε4) allele, encoding ApoE4, as the strongest genetic risk factor for late - onset Alzheimer's disease (LOAD) was a significant milestone [1]. Since then, numerous studies have delved into understanding how ApoE4 contributes to AD pathogenesis. Emerging epidemiological evidence indicates that ApoE4 influences β - amyloid (Aβ) deposition and clearance, although the exact molecular mechanisms remain elusive [1].

Early research on AD genetics also involved twin studies. The co - twin design in brain imaging has been used to investigate the associations of brain imaging markers of Alzheimer's disease and cognition. These studies, by controlling for genetic and environmental confounding, have provided insights into the causality of brain - cognition associations in AD [2]. Additionally, the role of protein prenylation in AD has been explored. Prenyltransferases, which post - translationally modify proteins, are being considered as potential drug targets in AD, as protein prenylation has been linked to the disease [3]. Over the years, the understanding of AD genetics has evolved from identifying single risk factors like ApoE4 to exploring complex gene - gene and gene - environment interactions.

Key genes implicated in Alzheimer's disease

Multiple genes have been identified as key players in Alzheimer's disease. Genes such as MAPT, APP, NCSTN, and BACE1 have shown potential as diagnostic markers. A study focused on these genes to build blood classifiers for AD. Using a combined model with measures of blood pressure, serum glucose, cholesterol, triglyceride levels, and RT - PCR expression levels of APP, NCSTN, and BACE1 in peripheral blood mononuclear cells, it was possible to differentially diagnose AD with up to 94.4% accuracy and 100% specificity in an independent sample [4].

In animal models, such as the Ts65Dn mice which mimic aspects of Down syndrome and early - onset AD, genes related to AD have been studied. PCR array analysis of the hippocampus of Ts65Dn mice revealed differential expression of genes like Nae1, APP, and Mapt compared to normal mice. Nae1 was decreased significantly, while APP and Mapt were increased, suggesting their potential

role in the disease process [5]. Bioinformatic analysis of transcriptome datasets for the hippocampus of AD patients has also identified critical genes and pathways. For example, genes involved in oxidative phosphorylation and pathways related to Parkinson's disease, Huntington's disease, and Alzheimer's disease were found to be significant, providing potential targets for AD therapies [6].

Genetic risk factors and their impact on Alzheimer's disease

Genetic risk factors significantly influence the development and progression of Alzheimer's disease. Traumatic brain injury (TBI) has been associated with an increased risk of AD. Epidemiological literature suggests that a single moderate - to - severe TBI may accelerate neurodegeneration and increase the risk of AD, although the pathologic phenotype may differ from sporadic AD [7]. Glutathione S - transferases (GSTs) polymorphisms have been investigated as candidate genetic risk factors for AD. However, a meta - analysis suggested null associations between polymorphisms of GSTM1, GSTT1, GSTM3, GSTP1, GSTO1 and AD risk, indicating that GSTs variants may not impact the morbidity of AD [8].

The ApoE4 allele is a well - known genetic risk factor. High - fat diet has been shown to affect ApoE levels in an isoform - dependent manner. In ApoE3 targeted replacement mice, high - fat diet caused a reduction of hippocampal ApoE levels, while the ketogenic diet had no effect. This finding suggests that dietary interventions for AD should consider ApoE genotype [9]. Genome - wide association studies have also identified other genes such as PICALM, BIN1, CD2AP, SORL1, and PLD3 as genetic risk factors in LOAD. These genes are implicated in Aβ42 production, specifically through the regulation of the endocytic trafficking of the amyloid precursor protein (APP) and/or its secretases [10].

EPIDEMIOLOGY OF ALZHEIMER'S DISEASE AND GENETIC INFLUENCES

Prevalence of Alzheimer's disease in genetically predisposed populations

The prevalence of Alzheimer's disease varies in genetically predisposed populations. In a study of a cohort from Liguria, Italy, genetic risk factors associated with early and late - onset Alzheimer's disease were analyzed. No significant association was found between the analyzed LOAD risk factors and AD or AD + MCI status after Bonferroni correction, although some potentially protective haplotypes and nominal associations were observed [11].

In the Ecuadorian population, a case - control study investigated the prevalence of Cystatin C (CST3), Cathepsin D (CTSD), and Manganese superoxide dismutase (MnSOD) amino - acid - altering polymorphisms and their influence on AD. A positive association was found between a CTSD polymorphism (Ala224Val) and the development of AD, while the other polymorphisms did not show significant associations [12]. In the Tibetan population of the Qinghai - Tibet plateau, the prevalence of AD was 1.33% among individuals aged > 60 years. The CLU haplotypes at rs9331888 and regular mind - body religious meditative activities were negatively correlated with AD [13].

Genetic epidemiology studies in Alzheimer's disease

Genetic epidemiology studies in AD have explored various aspects. A study investigated the genetic overlap between AD and immune - mediated diseases. Eight single - nucleotide polymorphisms were associated with both AD and immune - mediated diseases, suggesting that immune system processes influence AD pathogenesis and progression [14].

In the Atherosclerosis Risk in Communities (ARIC) study, the association between twenty single nucleotide polymorphisms identified in genome - wide association analyses of AD and cognitive change in middle - aged adults was examined. Some variants were nominally associated with change in cognitive function tests, although replication is required to establish a discernible influence [15]. In the PATH Through Life Study, 12 SNPs were significantly associated with baseline cognitive performance, linear rate of change, or quadratic rate of change in non - demented older Australians. A weighted genetic risk score was also associated with linear rate of change in episodic memory and information processing speed, suggesting that some AD - related SNPs may be associated with non - clinical cognitive decline [16].

Population genetics and Alzheimer's disease risk

Population genetics plays a role in understanding Alzheimer's disease risk. Analysis of next - generation sequencing data has revealed natural selection footprints in noncoding DNA sequences. Some noncoding sequence variants associated with diseases like AD showed signatures of positive selection, while the majority showed signatures of negative selection, indicating the functional importance of these noncoding elements in disease etiology [17].

In the Chinese population, a study investigated known AD - associated variants. The SORL1 gene was associated with AD, and a polygenic risk score (PRS) was developed and associated with AD risk, cognitive status, and AD -

related endophenotypes. This suggests that the PRS model can predict AD risk and cognitive status in this population [18]. A study on APOE haplotypes in healthy subjects from worldwide macro - areas elucidated the distribution of APOE variants and haplotypes, which can be leveraged for ancestry - informed screenings in relation to AD and other diseases [19].

PATHOPHYSIOLOGICAL MECHANISMS OF ALZHEIMER'S DISEASE GENES

Role of amyloid precursor protein (APP) in Alzheimer's disease

The amyloid precursor protein (APP) plays a central role in Alzheimer's disease. Misprocessing of APP is one of the major causes of AD. APP comprises an extracellular region, a transmembrane helix, and a cytoplasmic tail. The crystal structure of an APP/talin1 complex has been reported, identifying a new way to couple the cytoskeletal machinery to synaptic sites through APP. Talin1 depletion had a dramatic effect on APP processing in cells, suggesting a mechanical basis for AD [20].

In AD mouse models, such as the APP/PS1 transgenic mice, APP accumulation leads to amyloid - β (Aβ) deposition and subsequent neuroinflammation. Quetiapine, an antipsychotic drug, has been shown to attenuate glial activation and pro - inflammatory cytokines in APP/PS1 transgenic mice via inhibition of the nuclear factor - κB pathway. This indicates that APP - related inflammation can be modulated, potentially providing a therapeutic approach [21]. Additionally, the gut microbiota may also be related to APP - mediated AD pathology. A study on APP/PS1 transgenic mice found that there were substantial changes in gut microbial composition, and a strong correlation emerged between the gut microbiota and kidney metabolism, suggesting new directions for therapeutic strategies [22].

Tau protein and its genetic regulation in Alzheimer's disease

Tau protein and its genetic regulation are crucial in Alzheimer's disease. The GSK3β gene has been associated with pathological functions in neurodegenerative diseases. It is involved in the hyperphosphorylation of microtubule - associated tau protein, leading to the formation of neurofibrillary tangles (NFTs). Analysis of the human GSK3β promoter in AD patients showed overall hypomethylation of CpG and non - CpG cytosine residues, and GSK3β mRNA was overexpressed only in patients with initial AD, although there was no effect on the protein levels [23].

MicroRNAs (miRNAs) also play a role in tauopathies. miR - 132, for example, plays a critical role in regulating TAU protein levels and is important for preventing tau protein aggregation that causes Alzheimer's disease. Music - listening has been shown to upregulate miR - 132 in listeners with high musical aptitude, suggesting a potential link between environmental factors and tau regulation [24]. In addition, N6 - methyladenosine (m6A) methylation of promoter antisense RNAs (paRNAs) has been found to be involved in AD. A paRNA produced adjacent to the MAPT locus, which encodes the Tau protein, is enriched in neurons, and m6A positively controls its expression. This paRNA promotes the expression of genes related to neuronal and synaptic functions, playing a neuroprotective role against excitotoxicity [25].

Genetic contributions to neuroinflammation in Alzheimer's disease

Genetic factors contribute significantly to neuroinflammation in Alzheimer's disease. The 5 - lipoxygenase (5 - LOX) pathway has been implicated in the molecular pathology of AD. 5 - LOX and its downstream leukotriene metabolites are important modulators of oxidation and inflammation. In vivo evidence using murine knock - out models has shown that the 5 - LOX pathway is involved in the metabolism of amyloid - β and tau, suggesting that targeting this pathway could lead to therapeutics for AD [26]. Mutations in the triggering receptor expressed on myeloid cells 2 (TREM2) are associated with an increased risk of AD. Disease - associated mutations of TREM2 alter the processing of N - linked oligosaccharides in the Golgi apparatus, affecting the trafficking of TREM2 to the plasma membrane and its normal functions. This impairment may contribute to the disease by inhibiting normal functions in the plasma membrane [27]. Quetiapine has been shown to attenuate glial activation and reduce pro - inflammatory cytokines in APP/PS1 transgenic mice by inhibiting the nuclear factor - κB pathway, highlighting the role of genetic - related inflammation in AD and potential therapeutic targets [21].

DIAGNOSTIC ADVANCES IN ALZHEIMER'S DISEASE GENETICS

Genetic biomarkers for early detection of Alzheimer's disease

Genetic biomarkers hold promise for the early detection of Alzheimer's disease. In a Croatian cohort, an assessment of whether six MAPT haplotype - tagging polymorphisms and MAPT haplotypes are associated with AD pathology, as measured by cerebrospinal fluid (CSF) AD biomarkers, was conducted. Significant increases in t - tau

and p - tau CSF levels were found in patients with certain MAPT genotypes and haplotypes, indicating that MAPT haplotype - tagging polymorphisms and MAPT haplotypes should be further tested as potential genetic biomarkers of AD [28]. A novel deep - learning classifier, c - Diadem, was developed to identify potential blood - based genetic markers of mild cognitive impairment (MCI)/AD. Using SNPs and microarray data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), the model showed superior performance compared to previous models. SHAP scores identified SNPs in PRKCZ, PLCB1, and ITPR2, as well as the expression of HLA - DQB1, EIF1AY, HLA - DQA1, and ZFP57 as having more impact on model predictions, providing potential insights into disease mechanisms and new diagnostic markers [29].

Advances in genetic testing for Alzheimer's disease

Advances in genetic testing for Alzheimer's disease have been made. CNV - Finder, a novel pipeline integrating deep - learning techniques on array data, has been developed to expedite the large - scale identification of copy number variations (CNVs) within predefined genomic regions relevant to neurological diseases including AD. By training on expert - annotated samples and validating across diverse cohorts, it can accurately detect deletions and duplications in genes such as APP, which may be relevant to AD [30]. In - silico methods have also been used to analyze AD - associated non - synonymous single nucleotide polymorphisms (nsSNPs). Using advanced computational biology methods, five deleterious nsSNPs were identified in ACKR2(V41A), APOE(R176C), ATP8B4(G395S), LAMB2(E987K), and TOMM40(R239W). These findings provide insights into the pathogenic mechanisms of AD, although further in vivo and in vitro experiments are needed for validation [31].

Role of genomics in Alzheimer's disease diagnosis

Genomics has a significant role in Alzheimer's disease diagnosis. Genome - wide association and whole - exome - and whole - genome sequencing studies have mapped more than 20 disease - associated loci, providing insights into the molecular pathways involved in AD pathogenesis and potential therapeutic targets. These genomic findings may be used for the diagnosis and prognosis of AD, although challenges such as the complex nature of the disease and the need for further validation remain [32,33]. The NeuroArray, a custom CGH microarray, has been developed to screen and investigate the role of recurring genomic aberrations in patients with confirmed or suspected AD. It can identify chromosomal abnormalities in a large panel of AD - related genes with high sensitivity, making it a valid tool for clinical diagnosis [34]. Spatial - anatomic similarity - based methods have also been incorporated into the voxel - wise genome - wide association study (VGWAS) framework for AD biomarker detection. This approach can successfully detect new risk genes and clusters of AD, providing a new way to understand the underlying pathological mechanism of AD [35].

THERAPEUTIC STRATEGIES TARGETING ALZHEIMER'S DISEASE GENES

Gene therapy approaches for Alzheimer's disease

Gene therapy approaches for Alzheimer's disease are being explored. Delivery of a transgene encoding FK506 - binding protein 12.6/1b (FKBP1b) to the hippocampus of aged rats reversed aging - related neuronal Ca2 + dysregulation and cognitive impairment. Immunohistochemistry and qRT - PCR confirmed hippocampal FKBP1b overexpression, and aged rats overexpressing FKBP1b showed enhanced spatial memory and reduced slow afterhyperpolarization magnitude, suggesting FKBP1b as a potential therapeutic target [36]. Recombinant adeno - associated viruses (rAAVs) are being used to model and develop gene - therapy approaches for AD. In a study, rAAV - based models were used to investigate AD in mice. These models can help in deciphering pathomechanisms and developing novel gene - therapy strategies. For example, gene therapy using rAAVs to deliver genes that modulate amyloid pathway intermediates, tau protein, or neurotrophin expression may offer potential treatment options for AD [37,38].

Pharmacogenomics and personalized medicine in Alzheimer's disease treatment

Pharmacogenomics has the potential to revolutionize Alzheimer's disease treatment. The CYP450 enzyme polymorphisms play a central role in the hepatic metabolism of many AD medications. For example, variability in CYP450 expression and activity affects the pharmacokinetics, efficacy, and safety of approved anti - AD drugs. Integrating pharmacogenomics into clinical practice, such as genotyping for CYP2D6, CYP2C9, CYP2C19, and CYP3A4, may enhance therapeutic precision, reduce adverse outcomes, and improve the quality of life in patients with AD [39,40]. The APOE genotype is also an important factor in pharmacogenomics for AD. APOE - 3 carriers are generally the best responders to certain drugs, while APOE - 4 carriers are the worst responders. Incorporating APOE genotyping into treatment decisions can optimize limited therapeutic resources and reduce unwanted side - effects. For example, in the treatment of AD with anti - dementia drugs, antipsychotics,

antidepressants, etc., pharmacogenetic screening prior to treatment can help in choosing the most appropriate drugs and dosages [41].

Emerging genetic therapies for Alzheimer's disease

Emerging genetic therapies for Alzheimer's disease show promise. Pre - clinical trials have targeted various aspects of AD pathophysiology, such as amyloid pathway intermediates and enzymes modulation, tau protein downregulation, APOE4 downregulation and APOE2 upregulation, neurotrophin expression, and inflammatory cytokine alteration [42]. There have been three completed human clinical trials for genetic therapy in AD patients, all of which upregulated nerve growth factor (NGF). Although the results were mixed, they provide valuable lessons for future research. Challenges such as delivering monogenic genetic therapies for complex polygenic disorders, risks associated with the dominant delivery method (intracranial injection), stability of genetic therapies in vivo, and poor translatability of pre - clinical AD models need to be overcome before genetic therapies can be successfully applied to AD [42].

CONTROVERSIES AND FUTURE DIRECTIONS IN ALZHEIMER'S DISEASE GENETICS

Ethical considerations in genetic testing for Alzheimer's disease

Ethical considerations in genetic testing for Alzheimer's disease are of great importance. In the context of deep brain stimulation (DBS) trials in patients with early - onset Alzheimer's disease (EOAD), appropriate patient selection and signing of informed consent for genetic testing are crucial. Since a portion of EOAD patients, especially those with autosomal - dominant mutations, have an atypical and more aggressive disease progression, ensuring that patients are well - informed about the potential risks and benefits of genetic testing is essential [43]. The impact of genetic test results on individuals also needs to be considered. While studies have found that the negative psychosocial impact of genetic test results on the individual is limited, pre/post - testing genetic counseling is emphasized. There is an urgent need for regulation, particularly in the direct - to - consumer (DTC) market, as interest in testing in this context is rapidly growing. Standardized protocols for disclosure should be developed, and ways to meet the growing need for genetic counseling should be found [44].

Debates on the role of genetics versus environment in Alzheimer's disease

The debate on the role of genetics versus environment in Alzheimer's disease is ongoing. While genetic factors, such as the APOE ε4 allele, are well - established risk factors for AD, environmental factors also play a significant role. Exposure to environmental contaminants, such as pesticides like dichlorodiphenyltrichloroethane (DDT), has been shown to increase Aβ levels by impairing the function of ABCA1 and IDE, suggesting a potential environmental contribution to AD pathogenesis [45]. On the other hand, studies on monozygotic twins discordant for AD have provided insights into the relative contributions of genes and environment. Voxel - based morphometry studies have suggested that genetic factors more largely control neocortical regions, whereas environmental factors more strongly affect medial temporal regions. This indicates that both genetic and environmental factors interact in complex ways to influence the development of AD [46].

Future research directions in Alzheimer's disease genetics

Future research in Alzheimer's disease genetics should focus on several areas. Next - generation sequencing (NGS) technologies, including whole - genome sequencing (WGS) and whole - exome sequencing (WES), have the potential to identify rare variants with large effect sizes, which could further our understanding of the genetic basis of AD. These technologies can be used to investigate the complex genetic architecture of AD and potentially identify new therapeutic targets [47]. Defining the dynamic neuroinflammatory phenotype (NIP) profile and pathways that underlie APOE - modulated chronic neuroinflammation is crucial. Since APOE4 is a major genetic risk factor and APOE - modulated Aβ - induced neuroinflammation is not well - understood, future studies in this area could lead to the development of APOE genotype - specific therapeutics [48]. Additionally, more research is needed to understand the complex interactions between genetic and environmental factors, as well as to develop better pre - clinical models that can accurately recapitulate the human disease for more effective translation of research findings into clinical applications.

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DATA AVAILABILITY DECLARATION

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author, [Hongjuan Dong], upon reasonable request.

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