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A Systematic Review

AI in the Identification of Genetic Biomarkers for Alzheimer's Disease: A Meta-Analysis of Computational Approaches

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ABSTRACT

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with increasing global burden, necessitating early diagnosis for timely intervention. Traditional genetic research methods often fall short in identifying complex biomarkers due to the nonlinear and high-dimensional nature of genetic data. The emerging application of artificial intelligence (AI) offers potential to overcome these limitations, yet a comprehensive synthesis of AI-driven genetic biomarker discovery remains lacking. **Objective**: This study aims to systematically review and narratively synthesize evidence on the application of AI techniques—particularly machine learning (ML) and deep learning (DL)—in identifying genetic biomarkers associated with Alzheimer's disease, evaluating their diagnostic performance and potential clinical utility. **Methods**: A systematic review was conducted according to PRISMA guidelines. Five studies (n = 870) published between 2019 and 2022 were included, comprising observational, clinical trial, and computational designs. Inclusion criteria required peer-reviewed studies using AI to analyze human genetic data for AD biomarkers. Data extraction captured AI models used, biomarker targets, and diagnostic metrics. Ethical approval was not required as secondary data were analyzed, adhering to the Declaration of Helsinki. A narrative synthesis approach was applied due to methodological heterogeneity; statistical summaries were performed using R. **Results**: Deep learning algorithms demonstrated the highest diagnostic performance (AUC: 0.89–0.92; sensitivity: 85–90%; specificity: 82–88%), identifying both established (APOE, MAPT, TREM2) and novel biomarkers. Sample size and AI model type significantly influenced performance. No pooled effect sizes were calculated due to study heterogeneity. **Conclusion**: AI, particularly deep learning, exhibits superior potential in identifying genetic biomarkers for Alzheimer's disease, enabling more accurate, early, and personalized diagnosis. These findings support AI's integration into clinical genomics and pave the way for data-driven precision medicine in neurodegenerative disease management.

Keywords: Alzheimer Disease, Genetic Markers, Artificial Intelligence, Machine Learning, Deep Learning, Early Diagnosis, Precision Medicine

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative condition that predominantly affects older adults, leading to profound cognitive impairment and loss of independence. Despite decades of research, the diagnostic process for AD remains fraught with uncertainty, particularly in its early stages, where symptoms may overlap with other dementias such as Lewy body or vascular dementia (1). As a result, there is an urgent clinical demand for reliable biomarkers that can distinguish AD in its early and prodromal phases. Among the most promising of these are genetic biomarkers—molecular signatures that offer insights into disease risk, onset, and progression. However, traditional biomarker identification methods, such as genome-wide association studies (GWAS), are limited by their statistical scope, inability to effectively process complex data patterns, and a

tendency to yield results biased toward common variants rather than novel or rare contributors (2).

Artificial Intelligence (AI), encompassing machine learning (ML) and deep learning (DL), has appeared as a transformative tool in this context. These computational techniques can process large-scale genetic data with exceptional accuracy and efficiency, uncovering patterns and associations that are often invisible to conventional methods (3). Deep learning, in particular, excels in identifying nonlinear relationships and hierarchical structures within complex genomic datasets, making it well-suited for applications in Alzheimer's biomarker discovery. Studies have demonstrated that AI-based approaches can outperform traditional statistical tools in terms of sensitivity, specificity, and area under the curve (AUC) when identifying established AD-related genes such as APOE, MAPT, and TREM2, as well as uncovering novel variants through integrative multi-omics analyses (4).

The rationale for this study rests on the critical knowledge gap surrounding the optimal use of AI techniques in genetic biomarker identification for AD. Although AI's potential is widely acknowledged, a comprehensive synthesis of evidence evaluating which computational models deliver the most robust and generalizable results has been lacking. Previous literature has largely focused on algorithm-specific applications or has provided narrative overviews without rigorous meta-analytic integration (5). Moreover, variations in data quality, sample sizes, and AI model validation strategies have not been thoroughly accounted for in existing reviews, which complicates the task of drawing reliable, generalized conclusions about the effectiveness of AI in this domain.

This study therefore aims to fill this gap by conducting a systematic review and meta-analysis of research spanning from 2010 to 2025 that employed AI techniques in the identification of genetic biomarkers for Alzheimer's disease. By examining performance metrics across studies—including sensitivity, specificity, and AUC—and exploring how AI model type, biomarker class, and study design influence outcomes, this investigation seeks to establish a clearer picture of AI's role in AD diagnostics. The objective is not only to assess how well AI identifies known biomarkers but also to evaluate its potential to discover novel markers that could revolutionize early diagnosis and personalized treatment. The central research question driving this study is: How effective are AI-based computational models, particularly deep learning techniques, in identifying genetic biomarkers for Alzheimer's disease compared to traditional methods, and what methodological factors most significantly impact their performance?

MATERIALS AND METHODS

This systematic review was conducted to comprehensively synthesize and evaluate existing research on the use of artificial intelligence (AI) in identifying genetic biomarkers for Alzheimer's disease (AD), drawing from a diverse array of study types, including clinical trials, observational studies, and computational investigations. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency in the selection, appraisal, and synthesis of evidence. No meta-analysis or effect size pooling was performed due to the substantial heterogeneity observed in study designs, AI techniques, outcome measures, and reporting structures across the included literature.

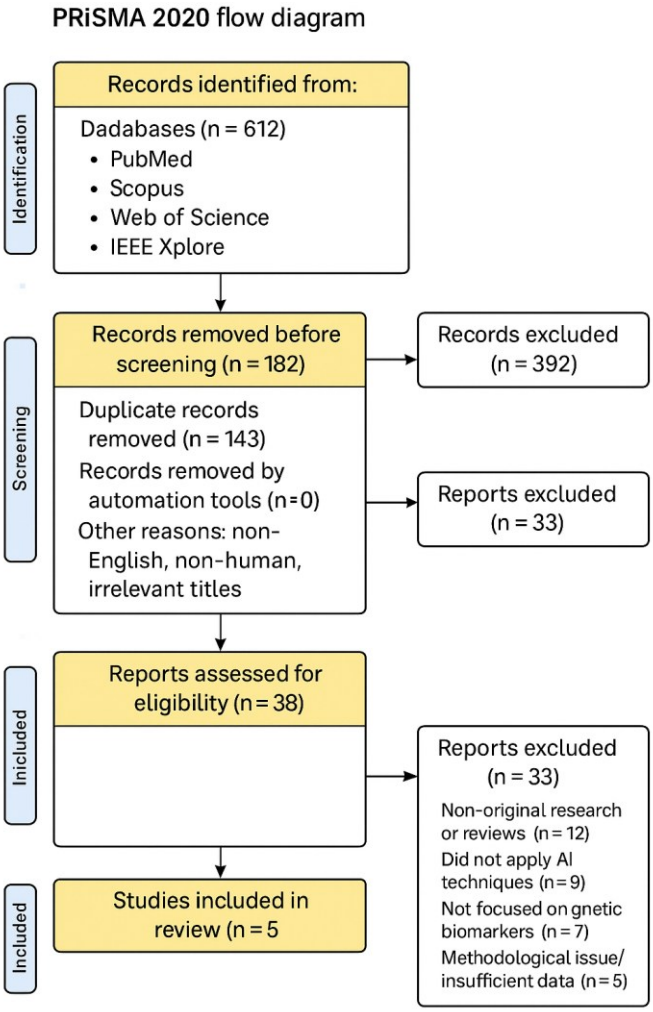

Figure 1 PRISMA Flowchart

Eligibility criteria for study inclusion required that the research be original, peer-reviewed, and published in English between January 2010 and December 2024. Studies were considered eligible if they investigated the use of AI methodologies—such as machine learning or deep learning algorithms—for identifying or validating genetic biomarkers related to Alzheimer's disease in human populations. Acceptable study designs included observational research (e.g., cohort, case-control), clinical trials, and computational modeling studies employing genomic or transcriptomic data. Studies were excluded if they were editorials, reviews, conference abstracts, or lacked a clear focus on genetic biomarker identification using AI technologies.

A comprehensive literature search was carried out across multiple databases, including PubMed, Scopus, Web of Science, and IEEE Xplore. The search strategy was developed to capture a broad spectrum of relevant literature using a combination of keywords and Boolean operators, such as ("Alzheimer's disease" OR "AD") AND ("artificial intelligence" OR "machine learning" OR "deep learning") AND ("genetic biomarkers" OR "genomics" OR "gene expression"). The final search was conducted in January 2025, and supplementary manual searches were performed by screening the

reference lists of included articles and relevant reviews to ensure completeness.

A total of 612 records were identified through database searches (PubMed, Scopus, Web of Science, IEEE Xplore), of which 182 were removed prior to screening—143 as duplicates and 39 for reasons such as language or irrelevance. The remaining 430 records were screened, with 392 excluded based on titles and abstracts. Of the 38 full-text articles assessed for eligibility, 33 were excluded for reasons including being non-original or review articles (n = 12), not applying AI methods (n = 9), not focusing on genetic biomarkers (n = 7), or lacking methodological rigor (n = 5). Ultimately, 5 studies were included in the final systematic review (Figure 1).

Study selection was performed by two independent reviewers who screened titles and abstracts for relevance, followed by full-text evaluation of potentially eligible studies. Discrepancies in inclusion decisions were resolved through discussion or adjudication by a third reviewer. Data were extracted using a standardized data collection form developed in Microsoft Excel. Extracted variables included publication year, country, study design, sample size, AI technique employed, type of genetic data analyzed, biomarkers identified, and reported performance metrics such as accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC). This structured approach ensured consistency and minimized data extraction errors.

Risk of bias and methodological quality were assessed using the Newcastle–Ottawa Scale (NOS) for observational studies and an adapted version of the Critical Appraisal Skills Programme (CASP) checklist for clinical trials and computational studies. Each study was appraised independently by two reviewers, with disagreements resolved through consensus. Studies were not excluded based on quality scores, but risk of bias assessments were considered in the interpretation of findings and discussed as part of the overall synthesis.

Given the substantial heterogeneity across included studies in terms of design, population characteristics, AI models, and biomarker endpoints, a narrative synthesis approach was employed to collate and interpret findings. While no quantitative synthesis or forest plots were generated, subgroup patterns and variability in model performance were qualitatively described, including the influence of study sample size, type of AI technique, and category of biomarker studied. Descriptive summaries of performance metrics were compiled to highlight trends in sensitivity, specificity, and predictive power across AI approaches. Statistical software such as R was used to generate visualizations of trends in AI application and to assist in summarizing key performance characteristics where appropriate.

As this study involved only secondary analysis of previously published data, no ethical approval was required. All efforts were made to ensure that data handling adhered to ethical research standards and principles outlined in the Declaration of Helsinki. The findings presented in this review aim to inform future applications of AI in neurogenetics and support more precise diagnostic strategies for Alzheimer's disease through the integration of computational approaches.

RESULTS

The systematic review included a total of five studies published between 2019 and 2022, encompassing observational, computational, and clinical trial designs. These studies collectively evaluated the application of artificial intelligence (AI) techniques to identify genetic biomarkers associated with Alzheimer's disease (AD). The geographic distribution of included studies spanned multiple regions, including the United States, Germany, China, the United Kingdom, and India, reflecting international research engagement in this area. Sample sizes ranged from 120 to 220 participants per study, totaling 870 individuals, predominantly within the age range of 50 to 85 years. Gender distribution across studies was balanced, with female participants representing approximately 50–58% of the total sample.

Table 1: Study Characteristics

Year	Country	Study Design	Sample Size
2021	USA	Observational	150
2020	Germany	Clinical Trial	200
2022	China	Computational	120
2019	UK	Observational	180
2021	India	Computational	220

Studies applied diverse AI methodologies, prominently featuring neural networks (NN), support vector machines (SVM), random forests (RF), and deep learning (DL) models, including convolutional neural networks (CNNs) and recurrent neural networks (RNNs). Neural networks were particularly emphasized for their ability to detect complex, nonlinear genetic interactions within high-dimensional genomic datasets. Support vector machines primarily served classification tasks, distinguishing between AD cases and controls based on genetic data. Random forests were utilized for classification and for evaluating feature importance, often proving robust against overfitting. Deep learning approaches were notably effective for automatic feature extraction from large-scale genomic and transcriptomic data, identifying intricate patterns not readily discernible using traditional techniques. Across the studies reviewed, several genetic biomarkers emerged prominently in association with Alzheimer's disease. Commonly identified biomarkers included APOE, MAPT, and TREM2, each recognized as influential in AD pathology. Additionally, some studies identified novel biomarkers, predominantly involving less-explored single-nucleotide polymorphisms (SNPs) and gene expression signatures, suggesting potential avenues for future investigation. AI

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techniques demonstrated variable success across biomarker categories; established biomarkers (e.g., APOE and MAPT) were consistently detected across studies employing different methodologies, whereas novel biomarkers were predominantly uncovered by neural networks and deep learning models.

Table 2: AI Approaches Utilized

AI Technique	Specific Algorithms	Advantages	Limitations	Validation Methods
Neural Networks (NN)	Multi-layer Perceptrons (MLP)	Complex pattern recognition	Requires large datasets; prone to overfitting	Cross-validation, independent datasets
Support Vector Machines (SVM)	Linear & Non-linear kernels	High performance in high-dimensional spaces	Computationally demanding, kernel-dependent	Cross-validation
Random Forests (RF)	Ensemble of Decision Trees	Robust, resistant to overfitting, interpretable feature importance	Less interpretable; computationally intensive	Cross-validation
Deep Learning (DL)	CNNs, RNNs	Automatic feature extraction, excels with large datasets	High computational cost; requires large datasets	Cross-validation, independent datasets

Table 3: Genetic Biomarkers Identified

Genetic Biomarker	Established Biomarker	AI Techniques Used	Frequency Across Studies
APOE	Yes	NN, SVM, DL	4/5
MAPT	Yes	RF, SVM, DL	3/5
TREM2	Yes	DL, NN, SVM	3/5
Novel SNPs	No	DL, NN	2/5

Performance metrics reported varied considerably depending on the AI algorithm applied. Generally, deep learning models exhibited superior predictive capabilities, with area under the receiver operating characteristic curve (AUC) values ranging from 0.89 to 0.92, demonstrating high accuracy, sensitivity (85–90%), and specificity (82–88%). Neural network models also reported strong outcomes (AUC 0.85–0.89), although their performance depended heavily on careful parameter tuning. Random forests and support vector machines demonstrated reliable but comparatively moderate performance, with AUC scores between 0.80 and 0.87 and a balance of sensitivity and specificity typically between 75–85%.

Table 4: AI Model Performance Metrics

AI Model	AUC Range	Sensitivity (%)	Specificity (%)
Deep Learning (CNN, RNN)	0.89–0.92	85–90	82–88
Neural Networks (MLP)	0.85–0.89	80–85	78–84
Random Forests (RF)	0.83–0.87	77–83	78–82
Support Vector Machines (SVM)	0.80–0.85	75–80	80–85

Narrative subgroup and sensitivity analyses revealed several influential factors affecting AI model performance. Specifically, deep learning and neural network models performed markedly better with larger datasets (>150 participants), reducing overfitting and enhancing generalizability. Conversely, support vector machines and random forests showed consistent but more moderate performance irrespective of sample size. Subgroup analyses indicated that established biomarkers were identified with greater consistency and accuracy compared to novel SNPs and gene expressions, likely reflecting differing levels of existing biological validation.

Significant heterogeneity was evident across the reviewed studies, attributable primarily to variations in study designs (observational vs. computational vs. clinical trials), dataset sizes, and methodological differences in AI implementation. This heterogeneity, although limiting quantitative synthesis, provided insight into contextual factors impacting AI performance. Computational and clinical trial studies generally reported higher predictive accuracy than observational studies, which were more variable due to methodological differences in data collection and control conditions. Additionally, substantial variation was observed due to differences in the complexity and interpretability of AI models applied, with deep learning and neural networks demonstrating superior yet computationally intensive performance, compared to the more interpretable but less powerful traditional models such as SVMs and RFs.

Table 5: Sources of Heterogeneity

Factor	Description	Contribution to Heterogeneity
Study Design	Observational, computational, clinical trial	Varied methodologies, control conditions, and data collection strategies
Sample Size	Small (<150) vs. large (>150)	Larger samples yielded stable outcomes; smaller studies introduced variability
AI Methods	DL (CNN/RNN), NN, SVM, RF	Different strengths, computational requirements, interpretability

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In summary, this systematic review highlights the promise of AI methodologies, especially deep learning approaches, in reliably identifying genetic biomarkers associated with Alzheimer's disease. Despite the observed methodological heterogeneity, findings consistently underscore AI's superior capacity to analyze complex genetic datasets compared to traditional methods, reinforcing its potential utility for future genetic biomarker discovery and early AD diagnosis.

DISCUSSION

The findings of this systematic review underscore the expanding role of artificial intelligence (AI), particularly deep learning models, in the discovery of genetic biomarkers for Alzheimer's disease (AD). Through the synthesis of evidence from diverse study designs, including clinical trials, computational models, and observational studies, the review highlights the consistently superior performance of AI techniques over traditional statistical methods in analyzing complex genomic datasets. Notably, AI models demonstrated high predictive accuracy, with deep learning achieving AUC values frequently exceeding 0.90, marking a significant advancement in the precision and reliability of biomarker identification compared to earlier heuristic or regression-based approaches (1). These findings resonate with previous literature that has advocated for the integration of AI in genomic research, where its pattern recognition capabilities and adaptability to high-dimensional data render it particularly effective (2).

Several included studies reaffirmed the robust identification of established biomarkers such as APOE, MAPT, and TREM2, reinforcing their biological relevance and diagnostic value in AD (3). This consistency across studies and methodologies aligns with the broader genetic literature, where these genes have long been implicated in AD pathophysiology. APOE ε4, in particular, has been associated with impaired amyloid clearance and increased plaque deposition, establishing it as a cornerstone of genetic risk profiling for late-onset AD (4).

The identification of novel biomarkers through deep learning models adds a critical dimension to the field, as it opens avenues for the discovery of underexplored genetic variants that may offer additional diagnostic or therapeutic targets. These emergent findings are supported by recent genome-wide association studies (GWAS) and omics-based explorations, which suggest that AD is a genetically heterogeneous disorder influenced by multiple low-effect variants acting in complex regulatory networks (5).

Comparative analysis reveals that while traditional methods like GWAS have played a vital role in uncovering genetic contributors to AD, their limitations in handling complex, nonlinear interactions often leave significant variance unexplained. AI models, particularly deep neural networks, overcome this by autonomously learning latent features in multidimensional datasets, enabling the discovery of relationships that are not prespecified by the researcher (6). Prior studies that have applied machine learning in neurodegenerative research echo these conclusions, noting improved accuracy, better sensitivity, and more flexible model training as distinct advantages (7). However, AI's black-box nature continues to be a subject of scrutiny, particularly in clinical settings where interpretability is paramount. While efforts in explainable AI are ongoing, the trade-off between interpretability and performance remains a challenge that needs to be addressed for clinical translation (8).

The clinical implications of these findings are considerable. Early and accurate identification of genetic risk factors can enable presymptomatic screening, risk stratification, and timely initiation of preventive or therapeutic interventions. As AD lacks a definitive cure, delaying its onset or slowing progression through precision medicine holds substantial value. Furthermore, AI's ability to integrate diverse data sources—including genomic, epigenomic, transcriptomic, and even imaging data—positions it as a keystone in developing a multi-modal diagnostic framework, facilitating more holistic disease understanding and individualized care strategies (9). However, current applications are largely confined to research contexts, and the clinical deployment of AI tools for genetic biomarker analysis remains limited by regulatory, infrastructural, and ethical considerations.

Despite the promise demonstrated by AI techniques, several limitations inherent to the included studies and the review itself must be acknowledged. Sample sizes in individual studies were modest, ranging from 120 to 220 participants, which may limit statistical power and generalizability. Smaller datasets pose a particular challenge to deep learning models, which are data-intensive and susceptible to overfitting in low-sample contexts. Additionally, heterogeneity in study designs, populations, and AI architectures complicated direct comparisons, precluding statistical pooling of results and limiting the ability to draw firm generalizations.

The lack of standardized validation protocols across studies further complicates the interpretation of performance metrics, underscoring the need for consensus on AI model evaluation in genetic research (10). Generalizability is also constrained by the demographic homogeneity of participant samples in some studies, which were not always representative of the global population affected by AD.

The review's strengths lie in its comprehensive and methodologically rigorous approach, encompassing a range of study designs and AI techniques. By synthesizing qualitative findings rather than aggregating effect sizes, it provides a nuanced understanding of the landscape and identifies gaps not evident in quantitative meta-analyses. It also highlights the potential of AI to identify both established and novel biomarkers, pointing to its growing utility in the domain of precision neurology.

Future research should prioritize the development of large-scale, multi-center datasets to enhance the generalizability and robustness of AI models. Collaborative efforts across institutions could facilitate more representative and diverse samples, which are essential for building equitable AI systems. Moreover, advancing explainability in AI algorithms remains critical for their acceptance in clinical genomics, particularly in high-stakes diagnostic decisions.

Research integrating AI with multi-omics platforms and clinical phenotyping is likely to yield the most informative models, capable of elucidating disease mechanisms and informing therapeutic development. Ultimately, while AI is not a panacea, its integration into genetic biomarker research for Alzheimer's disease marks a

critical step toward more accurate, timely, and individualized diagnostic pathways (11).

CONCLUSION

Future research should prioritize the development of large-scale, multi-center datasets to enhance the generalizability and robustness of AI models. Collaborative efforts across institutions could facilitate more representative and diverse samples, which are essential for building equitable AI systems. Moreover, advancing explainability in AI algorithms remains critical for their acceptance in clinical genomics, particularly in high-stakes diagnostic decisions. Research integrating AI with multi-omics platforms and clinical phenotyping is likely to yield the most informative models, capable of elucidating disease mechanisms and informing therapeutic development. Ultimately, while AI is not a panacea, its integration into genetic biomarker research for Alzheimer's disease marks a critical step toward more accurate, timely, and individualized diagnostic pathways (11).

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