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RESEARCH ARTICLE

LD-informed deep learning for Alzheimer's gene loci detection using WGS data

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Abstract

INTRODUCTION: The exponential growth of genomic datasets necessitates advanced analytical tools to effectively identify genetic loci from large-scale high throughput sequencing data. This study presents Deep-Block, a multi-stage deep learning framework that incorporates biological knowledge into its AI architecture to identify genetic regions as significantly associated with Alzheimer's disease (AD). The framework employs a three-stage approach: (1) genome segmentation based on linkage disequilibrium (LD) patterns, (2) selection of relevant LD blocks using sparse attention mechanisms, and (3) application of TabNet and Random Forest algorithms to quantify single nucleotide polymorphism (SNP) feature importance, thereby identifying genetic factors contributing to AD risk.

METHODS: The Deep-Block was applied to a large-scale whole genome sequencing (WGS) dataset from the Alzheimer's Disease Sequencing Project (ADSP), comprising 7416 non-Hispanic white (NHW) participants (3150 cognitively normal older adults (CN), 4266 AD).

RESULTS: 30,218 LD blocks were identified and then ranked based on their relevance with Alzheimer's disease. Subsequently, the Deep-Block identified novel SNPs within the top 1500 LD blocks and confirmed previously known variants, including *APOE* rs429358 and rs769449. Expression Quantitative Trait Loci (eQTL) analysis across 13 brain regions provided functional evidence for the identified variants. The results were cross-validated against established AD-associated loci from the European Alzheimer's and Dementia Biobank (EADB) and the GWAS catalog.

DISCUSSION: The Deep-Block framework effectively processes large-scale high throughput sequencing data while preserving SNP interactions during

dimensionality reduction, minimizing bias and information loss. The framework's findings are supported by tissue-specific eQTL evidence across brain regions, indicating the functional relevance of the identified variants. Additionally, the Deep-Block approach has identified both known and novel genetic variants, enhancing our understanding of the genetic architecture and demonstrating its potential for application in large-scale sequencing studies.

KEYWORDS
Alzheimer's disease, deep learning, genetic loci, imputation methods, linkage disequilibrium, whole-genome sequencing

Highlights

- Growing genomic datasets require advanced tools to identify genetic loci in sequencing.
- Deep-Block, a novel AI framework, was used to process large-scale ADSP WGS data.
- Deep-Block identified both known and novel AD-associated genetic loci.
- rs429358 (*APOE*) was key; rs11556505 (*TOMM40*), rs34342646 (*NECTIN2*) were significant.
- The AI framework uses biological knowledge to enhance detection of Alzheimer's loci.

1 | INTRODUCTION

The advancement of deep learning in artificial intelligence (AI) has introduced new frameworks for analyzing complex genetic inheritance patterns, enhancing the interpretation of genomic data.[1–4] For complex diseases such as Alzheimer's disease (AD), there is a critical need for advanced analytic tools provided by AI to decipher the complexities of human genetic makeup.[4–6] The complexity of genomic studies necessitates innovative and adaptive approaches that transcend traditional machine learning techniques to analyze and elucidate these intricate genetic interactions.[7,8] The high dimensionality and large sample sizes characteristic of genetic data in AD research underscore the necessity for methods capable of navigating the complex landscape.[9–11] While several machine learning-based dimensionality reduction methods have been proposed, they have encountered challenges such as loss of phenotypic association information during the reduction process, reproducibility issues, and data-dependent inconsistencies in results.[12–14]

Here, we present Deep-Block, a deep learning framework designed to address the complexities of genomic sequencing data through targeted analysis of whole genome sequencing (WGS) data. Deep-Block employs a linkage disequilibrium (LD) block-based approach to systematically identify significant genetic regions, aiming to preserve vital phenotypic associations and minimize the loss of genetic information crucial for understanding disease phenotypes. The framework incorporates advanced machine learning and genomic imputation techniques[15–17] to ensure a comprehensive dataset without any missing values for analysis. Furthermore, the integration of the TabNet model,[18,19] an attention-based neural network, enhances the process by providing a detailed assessment of feature importance within the genetic data, thus enriching the analysis. The calculation of Phenotype Influence Scores (PIS) offers additional insights into the genetic basis of the disease, informing future research directions. The framework includes Expression Quantitative Trait Loci (eQTL) analysis across multiple brain regions to examine the biological context of identified variants. Comparative analysis with conventional sliding window approaches was performed to evaluate the identification of AD-associated variants.

Application of Deep-Block to a large-scale WGS dataset from the Alzheimer's Disease Sequencing Project (ADSP) Release 3, comprising 7416 non-Hispanic white (NHW) participants, demonstrated its capacity to effectively manage complex genomic data and identify single nucleotide polymorphisms (SNPs) as associated with AD. The Deep-Block framework identified AD-associated genetic loci, including well-known AD SNPs such as apolipoprotein E (*APOE*) rs429358 and rs769449 and novel SNPs not previously reported in AD genetic association studies, particularly within the top-performing LD blocks. The identified variants were examined through tissue-specific expression analysis to investigate their potential relationship with AD pathogenesis.

2 | METHODS

2.1 | Data collection and quality control

The ADSP participants were classified as AD cases or cognitively normal controls based on a comprehensive diagnostic framework. AD diagnoses were established through clinical diagnostic criteria, including detailed medical history, cognitive evaluations, and neuropsychological testing. Where available, these clinical assessments were supplemented with biomarker data, including cerebrospinal fluid measurements of amyloid-beta and tau proteins, and neuroimaging data indicating amyloid deposition. The ADSP participants have whole-genome sequencing (WGS) data sequenced using multiple platforms, including IlluminaHiSeq2000 and IlluminaHiSeqXTen. This release (R3) includes 16,906 WGS, processed and curated as part of the project. The release contains CRAMs, gVCFs, and quality-controlled project-level VCFs (pVCFs) for autosomal biallelic single nucleotide variants (SNVs) and indels, along with structural variant (SV) calls generated by Manta, Smoove, and Strelka variant callers. The WGS data were called by the Genome Center for Alzheimer's Disease (GCAD) using VCPA 1.1, a functionally equivalent CCDG/TOPMed pipeline. WGS data underwent comprehensive quality control (QC) procedures, including SNP call rates > 95%, Hardy–Weinberg equilibrium p-values $< 1 \times 10^{-6}$, minor allele frequencies (MAF) > 1%, absence of sex mismatches, and sample call rates > 95%. To mitigate false associations due to population stratification, the study analyzed genome-wide genotyping data from 7416 NHW participants (3150 cognitively normal individuals [CN] and 4266 AD patients), encompassing 10,764,329 SNPs. The male sex ratio was 56.3% for AD patients (mean age 70.1 years) and 60.7% for CN individuals (mean age 80.2 years).

2.2 | Algorithm implementation and analysis

The Deep-Block framework employs a structured, three-stage process to analyze large-scale WGS data:

2.2.1 | Segmentation of whole genome into LD blocks

Following QC, the WGS dataset was segmented into LD blocks using Plink software (v1.90b6.21 64-bit). The parameters were set as follows: the LD measure was r^2 with a threshold of 0.9, window size of 50 variants, and maximum window physical size of 100 kilobases. LD blocks were then identified based on the genomic positions of SNPs and the extent of LD between adjacent SNPs. This configuration identified 30,218 LD Blocks, forming the basis for subsequent analyses.

Comparative analysis of segmentation approaches

To evaluate the effectiveness of the LD block-based segmentation approach, we conducted experiments with baseline methods using the top 1500 LD blocks. A sliding window approach[10] using fixed windows of 200 variants was implemented as the baseline for comparison. For each method, SNPs were prioritized based on their computed importance scores: Deep-Block with LD-based segmentation utilized PIS, while Random Forest and TabNet with fixed window segmentation used their respective feature importance metrics.

RESEARCH IN CONTEXT

1. **Systematic review**: A comprehensive literature review was conducted using PubMed and Google Scholar to identify studies on analytical tools for large-scale genomic data processing in Alzheimer's disease (AD) research. Previous studies have proposed various machine learning approaches, but challenges persist in areas such as information preservation during dimensionality reduction and result reproducibility.
2. **Interpretation**: The Deep-Block, a novel Deep Learning framework, identified AD-associated genetic loci, including both previously identified and novel single nucleotide polymorphisms (SNPs), leading to the identification of complex genetic patterns associated with AD that may have been overlooked in traditional genetic association methods, emphasizing the importance of advanced sequencing data analysis tools.
3. **Future directions**: Further research is needed to validate these findings across diverse populations. Additional areas for investigation include: (1) assessment of the Deep-Block framework's scalability to larger datasets, (2) functional validation of newly identified genetic loci, and (3) evaluation of this approach's applicability to other genetically complex diseases.

2.2.2 | Imputation of missing genotype data

Deep-Block utilizes machine learning approaches to impute missing genotype data within the LD blocks, a method supported by recent studies.[15–17] To identify the most suitable imputer for imputing missing genotype data, preliminary experiments were conducted on the *APOE* gene region within the ADSP WGS dataset, assuming SNPs of this region are contained within LD blocks. The ADSP R3 WGS data, comprising 16,869 individuals, included 793 variants from the *APOE* gene region. After QC, the missing data proportion in this region was 4.14E-03. For the performance assessment of imputers, the missing rate was artificially increased to 8.70E-03. The modified dataset was then processed using the TopMed Imputer, establishing a benchmark for comparing the efficiency of other imputation methods. Several imputers were used: 1-NN, 5-NN, 10-NN, GAN, Iterative, MissForest,[20] and Simple Imputer. All methods were applied to data with the same artificially increased proportion of missing genotype data to

ensure consistent evaluation. The scikit-learn package[21] was used for machine learning imputers and the GAIN package[22] for the GAN Imputer.

The Simple Imputer utilizes mean, median, or mode imputation to fill missing values with the most representative statistic of the available data. The k-Nearest Neighbors (k-NN) Imputers (1-NN, 5-NN, and 10-NN) leverage data point similarity to impute missing values based on the nearest neighbors' values. The GAN Imputer uses Generative Adversarial Networks to produce synthetic data mimicking the original data distribution, thus imputing missing values. The Iterative Imputer employs a round-robin approach, modeling each feature with missing values as a function of other features stepwise, capturing complex interactions, and dependencies. The MissForest Imputer utilizes a Random Forest approach, leveraging multiple decision trees to accurately predict missing values.

The performance of these methods was evaluated using five well-established metrics: accuracy, root mean squared error (RMSE), R-squared (R^2), mean absolute error (MAE), and normalized RMSE (NRMSE). The accuracy quantifies the proportion of correctly imputed values, directly reflecting an imputer's performance. The RMSE measures the average magnitude of imputation errors, providing a straightforward accuracy metric. The R^2 indicates the proportion of variance in the original data explained by the imputed data, offering insights into the imputation method's ability to preserve data structure. The MAE calculates the average absolute error between imputed and actual values, presenting error distribution without directional bias. The NRMSE normalizes RMSE to the dataset range, facilitating the performance comparison across differently scaled datasets.

2.2.3 | Identification of key LD blocks and phenotype association

The final stage identifies key LD blocks as significantly associated with the AD phenotype using TabNet, a deep learning model optimized for efficient tabular data processing.[18] TabNet was selected for its key advantages: simultaneous feature selection and engineering capabilities, interpretability through sparse attention mechanisms, and optimized architecture for large-scale tabular data processing. Given the high-dimensional nature of our genetic data (10,764,329 variants across 30,218 LD blocks), we implemented several key strategies to prevent overfitting. These include L1 regularization (lambda_sparse = 1e-3) to enforce sparsity in feature selection, learning rate scheduling with step decay (step_size = 10, gamma = 0.9) to optimize model convergence, and early stopping with patience monitoring to prevent unnecessary model complexity. For model validation, we maintained consistent 80/20 train-validation splits across all analyses. To validate this choice, we conducted a comparative analysis between TabNet and Random Forest approaches. The genome was segmented into 53,822 windows, each containing 200 variants, ensuring comprehensive coverage. Both models were applied to each window to assess prediction accuracy. The top 1500 windows were selected based on accuracy metrics for each model, and feature importance was calculated for 299,822 SNPs within these windows using each model's respective feature importance metrics. Incremental addition of top-ranked features showed that TabNet consistently outperformed Random Forest in area under the curve (AUC) scores (average AUC of 0.56 vs. 0.54), supporting our model selection. TabNet's architecture combines the interpretability of decision tree-based models with deep learning capabilities, featuring an encoder-decoder structure, feature transformers, and attentive transformers. TabNet's encoder processes raw tabular data, selecting relevant features through a sequential multi-step procedure using feature transformers. These transformers apply non-linear transformations to enhance the model's learning capabilities. The attentive transformer, a key encoder component, employs the sparsemax normalization function to focus selectively on the most relevant features, optimizing model interpretability and efficiency. This stage uses TabNet to identify LD Blocks with high phenotypic relevance, focusing on features critically associated with AD. TabNet's decoder reconstructs features from the original dataset, identifying key features within the top LD Blocks. This process assigns PIS to significant features, reflecting their phenotypic impact. The method integrates TabNet's feature importance metrics with the mean decrease impurity (MDI) metric from random Forest, offering a systematic approach to understanding genetic influences on phenotypic traits (Figure 1).

This approach combines the strengths of both metrics to identify the most significant AD-associated genetic markers, offering a robust method for detecting key genetic markers within LD blocks. The PIS is calculated using the following combined formula:

$$\mathrm{PIS}_j = I \cdot M_{\mathrm{agg}-b,j} + (1 - I) \cdot \mathrm{MDI}_j$$

where I is an indicator variable that is automatically set to 1 when the TabNet model yields a higher predictive accuracy in phenotype-related classification using previously selected features, and is automatically set to 0 when the Random Forest algorithm shows superior performance in the same task. $M_{\mathrm{agg}-b,j}$, where b represents the batch index for the current training iteration, the feature importance from the TabNet model, represents the aggregate feature importance mask for the j-th feature. The calculation uses the total number of decision steps (N), the learning rate at each decision step ($\eta_b[i]$), and a binary mask ($M_{b,j}[i]$) that is set to 1 if the j-th feature is utilized at the i-th decision step, and 0 otherwise. Here, D represents the total number of features. The corresponding formula is as follows:

$$M_{\mathrm{agg}-b,j} \frac{\sum_{i=1}^{N} \eta_b[i] M_{b,j}[i]}{\sum_{j=1}^{D} \sum_{i=1}^{N} \eta_b[i] M_{b,j}[i]}$$

MDI_j, the MDI from the random Forest algorithm, quantifies the impurity reduction for a specific SNP (SNP_j). This calculation encompasses the total number of decision trees in the model (N_{trees}), each tree (t), and the node (i), using SNP_j for splitting, includes the number of samples at node i before the splitting (n_i^t) and the impurity reduction

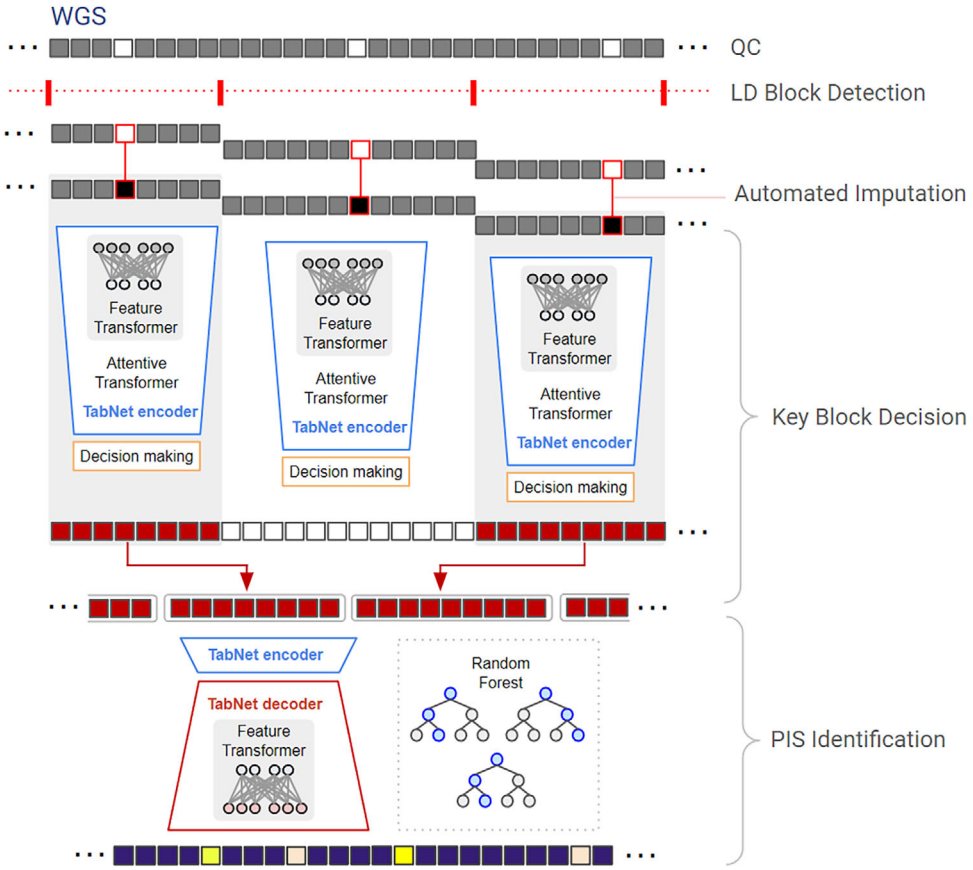

FIGURE 1 Overview of the Deep-Block framework. This figure illustrates the sequential stages of the Deep-Block framework used in the analysis of large-scale WGS data for AD. The process initiates with the QC procedure of WGS data, ensuring the integrity and reliability of the genetic information. Subsequently, the data is organized into LD blocks, indicated by red dotted lines, which reflect the partitioning based on LD parameters. The next phase, Automated imputation, is visualized as various modules corresponding to different machine learning-based imputation techniques each tasked with estimating and inputting missing genomic data. Following imputation, the TabNet encoder's role in decision-making is depicted, using feature transformers and attentive transformers to select and prioritize LD blocks that show significant associations with AD. The final element of the diagram focuses on the identification of the PIS using the TabNet decoder in conjunction with random forest metrics. AD, Alzheimer's disease; LD, linkage disequilibrium; PIS, Phenotype Influence Score; QC, quality control; WGS, whole genome sequencing.

at this node ($\Delta i(s_i^t)$). The MDI is calculated as follows:

$$\mathrm{MDI}_j = \frac{I}{N_{\mathrm{trees}}} \sum_{t=1}^{N_{\mathrm{trees}}} \sum_{i \in I_j^t} \frac{n_i^t}{n_{\mathrm{root}}^t} \Delta i\left(s_i^t\right)$$

2.3 | Functional analysis and annotation

We employed multiple approaches to characterize the functional implications of identified variants. The GTEx v10 database was used to identify eQTL signals across 13 brain-specific tissues, including the hypothalamus, hippocampus, cerebellum, cortex, nucleus accumbens, substantia nigra, anterior cingulate cortex, putamen, amygdala, cerebellar hemisphere, frontal cortex, spinal cord, and caudate. Statistical significance was assessed at $p < 0.05$. The variant effect predictor (VEP) with GRCh38 human genome assembly and ANNOVAR were used to determine the genomic context of the variants.

3 | RESULTS

This study analyzed large-scale WGS data from the ADSP, comprising 7416 NHW individuals (4266 with AD and 3150 cognitively normal older adults [CN]). After QC procedures, several imputation methods were comparatively evaluated: Simple, GAN, 1-NN, 5-NN, 10-NN, Iterative, MissForest, and TopMed Imputers. The assessment utilized metrics including accuracy, RMSE, R^2, MAE, and normalized RMSE (NRMSE).

The MissForest Imputer demonstrated superior performance among the machine learning-based methods, achieving the highest accuracy (0.999359), lowest RMSE (0.0039), and highest R^2 (0.9993). The 5-NN and 10-NN Imputers also performed well, with accuracy rates of 0.999734 and 0.999626, R^2 values of 0.9993, and RMSEs of 0.004 and 0.0041, respectively. The TopMed imputation server achieved an accuracy of 0.996416, RMSE of 0.0047, and R^2 of 0.9081. While effective in reducing RMSE, it showed a lower capacity to

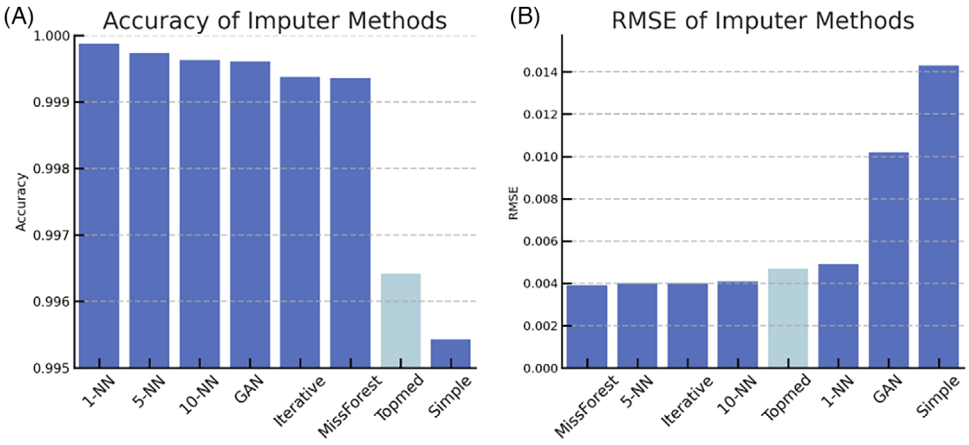

FIGURE 2 Comparative performance of imputation methods in WGS data. (A) Illustrates the accuracy for several imputation methods, which reflects the proportion of correctly imputed genotypes to the total number of predictions made. A value closer to one denotes a higher rate of correct imputations. In this analysis, the 1-NN Imputer exhibits the highest accuracy, while the Simple Imputer shows the least accuracy, pointing to a greater discrepancy in its predictions. (B) Displays the RMSE across the imputation methods, a metric for quantifying the average errors in the predicted values. The lower the RMSE, the more accurate the imputation. Here, the MissForest Imputer emerges as the most accurate with the smallest RMSE, while the Simple Imputer displays the largest RMSE, indicative of lower accuracy. The results of the Topmed Imputer were not as pronounced, falling behind with lower accuracy and a higher RMSE than several other imputers. RMSE, root mean squared error; WGS, whole genome sequencing.

TABLE 1 Comparison of imputation efficacies of imputation methods

Imputer method	Accuracy	RMSE	R^2	MAE	NRMSE
1-NN Imputer	0.999875	0.0049	0.9989	0	0.0049
5-NN Imputer	0.999734	0.004	0.9993	0	0.004
10-NN Imputer	0.999626	0.0041	0.9993	0.0001	0.0041
GAN Imputer	0.999606	0.0102	0.9981	0.0002	0.0102
Iterative Imputer	0.999373	0.004	0.9993	0.0001	0.004
MissForest Imputer	0.999359	0.0039	0.9993	0	0.0039
Topmed Imputer	0.996416	0.0047	0.9081	0.0002	0.0047
Simple Imputer	0.995432	0.0143	0.9965	0.0006	0.0143

Note: The table shows performance metrics for several imputation methods of missing genotypes. The accuracy measures the proportion of correctly imputed genotypes, where the 1-NN Imputer ranks the highest, suggesting the greatest precision in imputation among the methods. The RMSE shows the MissForest Imputer as the most accurate, with the smallest values indicating minimal deviation from actual data. R^2 values for the 5-NN, 10-NN, Iterative, and MissForest Imputers indicate that these models account for a significant portion of the variance, suggesting a strong correlation with the observed data. The MAE is lowest for the 1-NN, 5-NN, and MissForest Imputers, indicating higher precision. The NRMSE further confirms the MissForest Imputer's superior performance. Overall, the MissForest Imputer exhibits the highest precision in imputation of missing genotypes.
Abbreviations: MAE, mean absolute error; NRMSE, normalized root mean squared error; R^2, R-squared; RMSE, root mean squared error.

capture dataset variance compared to the leading machine learning methods (Figure 2 and Table 1).

Computation time for imputation methods was crucial due to the large-scale WGS data. Table S1 shows that the MissForest Imputer required up to 327 s for the largest block size, significantly longer than the 5-NN Imputer, which processed the same block in just over 50 ms. Balancing imputation accuracy and processing efficiency, the 5-NN Imputer was selected as the most suitable imputation method for our dataset. This choice was based on its high accuracy, and fast LD blocks were determined using Plink, resulting in 30,218 LD blocks with an average size of 388 genetic variants. Genomic regions not covered by LD blocks, comprising only 0.19% of the genome, were excluded from the analysis due to their negligible size. Figure 3B demonstrates the correlation between the number of blocks per chromosome and chromosome length. TabNet was then applied to the LD blocks to assess phenotype prediction accuracy using a binary classification model. Blocks were ranked based on prediction accuracy, and as the number of blocks increased, the analysis showed that the number of important features with non-zero TabNet feature importance did not increase significantly. Figure 3A illustrates this by depicting genetic variants within the key blocks as blue bars. The analysis extended up to 1500 blocks, revealing a plateau in the count of important features, indicating that the critical variants for phenotype prediction were already captured within the initial top blocks. This suggests that further analysis beyond these blocks may not provide additional meaningful insights.

To evaluate our LD block-based approach, we conducted a comparison with baseline segmentation methods using the top 1500 LD blocks. For each method, we incrementally selected SNPs based on their importance scores and assessed their predictive performance. Analysis showed that the Deep-Block framework achieved an average AUC of 0.66, while fixed sliding window-based approaches using Random Forest and TabNet showed average AUCs of 0.54 and 0.56, respectively. This pattern was consistent across different numbers of selected SNPs, as visualized in Figure 4A, which presents the AUC scores according to the number of SNPs used in the analysis for each method.

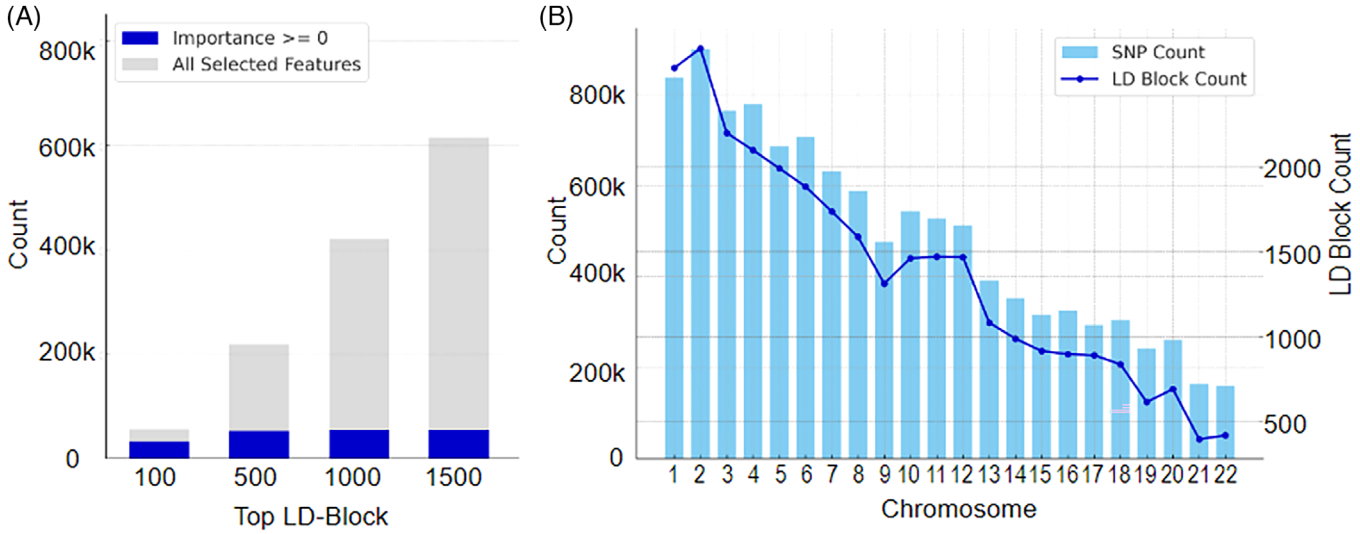

FIGURE 3 Feature importance and distribution across LD blocks in the ADSP WGS Dataset. (A) The analysis determined the feature importance using TabNet for the top 100–1500 LD blocks. The blue bars represent genetic variants within these blocks, where TabNet was assigned a feature importance greater than zero, indicating their relevance in phenotype prediction. The gray bars indicate all selected features, regardless of their importance score. The steady count of important features across increasing block ranks suggests that the most critical variants for phenotype prediction were concentrated in the top blocks. (B) Visualizes the distribution of LD blocks and SNP counts across chromosomes. The bar chart demonstrates that the number of LD blocks and SNPs is proportionate to the chromosome length, with larger chromosomes containing more blocks. ADSP, Alzheimer's Disease Sequencing Project; LD, linkage disequilibrium; SNPs, single nucleotide polymorphisms; WGS, whole genome sequencing.

The study analyzed 615,282 genetic variants within the top 1500 blocks, calculating the PIS for each genetic variant using the methodology outlined in the Methods section. Table 2 presents the top 30 genetic variants with the highest PIS. The SNP rs429358 within the *APOE* gene on chromosome 19, a well-known AD risk SNP,[23] demonstrated the highest importance score. Other high-importance SNPs on chromosome 19 include rs11556505 in *TOMM40*[24]) and rs34342646 in *NECTIN2*,[25] further emphasizing the relevance of chromosome 19 in AD. The study also confirmed previously reported AD-associated SNPs, including rs5117 and rs483082 in *APOC1*, and rs10414043 (*APOC1*), rs10119 (*TOMM40*), and rs71352238 (*TOMM40*).

In addition to confirming the importance of known genes, this study identified novel high-importance SNPs not previously identified in genetic association studies for AD, particularly within the top 30 variants. Notably, the study identified novel variants such as rs200986288, rs199988716, and rs202143966. Additionally, previously unreported genes associated with AD were identified, including *LOC107984083* (rs78790997) and *LOC728339* (rs75997270).

Figure 4B displays vertically aligned, symmetrical Manhattan plots (Miami plot) from two genetic association analysis methods: Deep-Block and Plink. The upper plot depicts the PIS derived from Deep-Block, while the lower plot shows the statistical significance levels (−log10 *p*-value) obtained using Plink across all chromosomes. Both plots arrange chromosomes along the *x*-axis, offering a chromosomal position view of the analyzed genomic variants. Each plot highlights the top 40 genetic variants using color-coded dots: red for the top 1–10 genetic variants, blue for the top 11–20 genetic variants, green for the top 21–30 genetic variants, and gray for the top 31–40 genetic variants. Of note, the Deep-Block approach identified the same genetic variants that the Plink identified as well as novel genetic variants that the Plink could not identify.

To contextualize the Deep-Block findings, the identified loci were compared to established AD-linked genetic loci reported in the European Alzheimer's and Dementia Biobank (EADB) and the recently updated GWAS catalog.[26] The validation process benefited from ancestral homogeneity, as both our study cohort (NHW participants) and the comparative databases are predominantly of European descent, ensuring methodological consistency in the assessment of our framework's performance. The analysis aligned with 15 genetic loci from the GWAS catalog, distributed across various tiers (3 in Tier1, 1 in Tier2, 2 in Tier3, 2 unverified, and 3 in the "Other" category), as detailed in Table S1. This comparison excluded the well-studied *APOE*, *TOMM40/APOC1/NECTIN2* loci to focus on other significant genetic associations. The results were also compared against databases referenced in the GWAS catalog, including IGAP2,[27] PGC1,[28] IGAP2+UKB,[29] GR@ACE,[30] PGC2,[31] and EADB.[32] Table S2 highlights Tier1 genes *ABCA7*, *BIN1*, and *CR1*, identified in multiple studies. This confirms the Deep-Block method's relevance to known AD genetic markers and indicates both confirmatory and potentially novel genetic associations with the disease.

4 | DISCUSSION

This study developed and applied the Deep-Block framework to large-scale WGS data from the ADSP to investigate the genetic

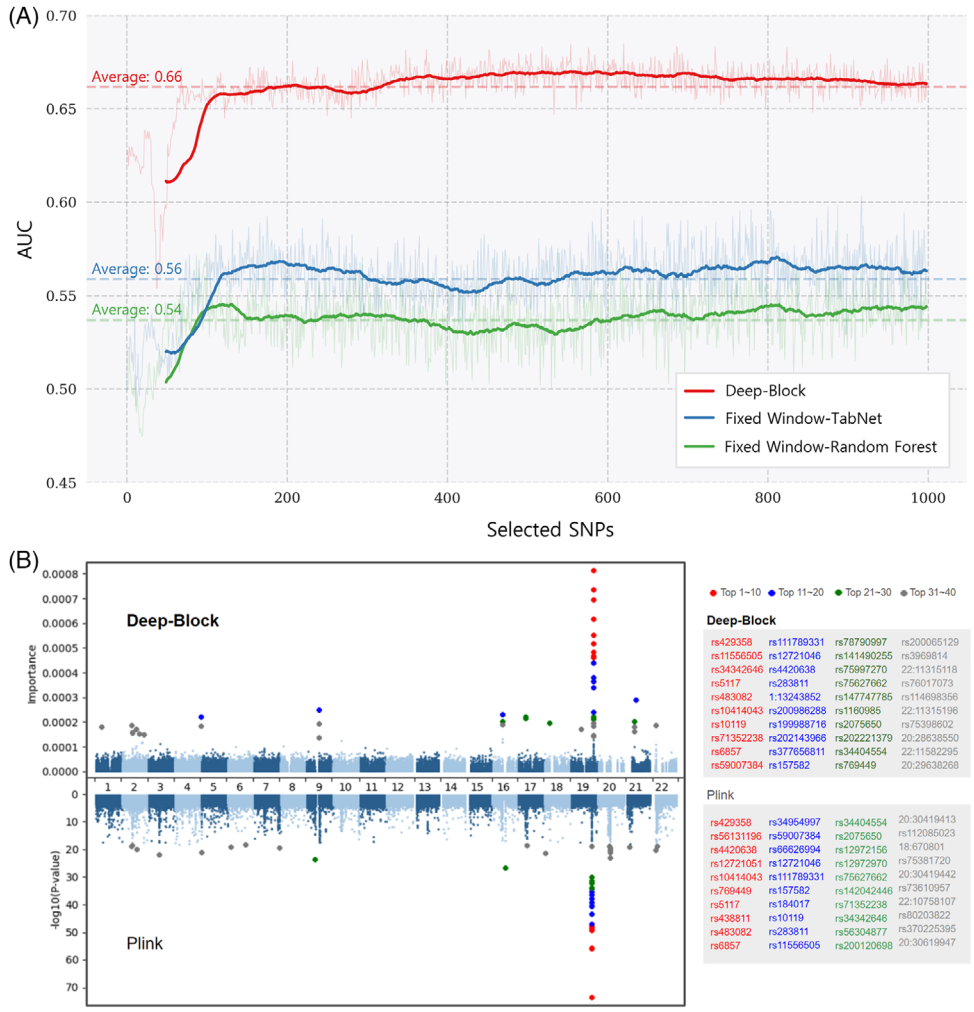

FIGURE 4 Performance and genomic analysis of Deep-Block framework. (A) Performance comparison between different genomic segmentation approaches, showing AUC scores based on selected SNPs from the top 1500 LD blocks. Lines represent smoothed AUC scores for Deep-Block with LD-based segmentation (red), TabNet (blue), and random forest (green) with fixed window approaches. (B) Miami plot comparing genetic association statistics between Deep-Block (upper) and Plink (lower). The plots display genome-wide SNP significance, with chromosomes listed numerically on the horizontal axis. Color-coding indicates significance ranking: red (top 1–10), blue (11–20), green (21–30), and gray (31–40), with a side panel listing SNPs in each category. AUC, area under the curve; LD, linkage disequilibrium; SNPs, single nucleotide polymorphisms.

basis of AD. The approach centered on utilizing LD blocks combined with automated imputation to improve the accuracy of genetic analysis. The PIS-based variant prioritization identified known AD-associated variants, with PIS values of 8.00E-04, 7.23E-04, and 6.85E-04 observed for established variants in *APOE* (rs429358), *TOMM40* (rs11556505), and *NECTIN2* (rs34342646) genes, respectively (Table 2). To facilitate comprehensive analysis of genetic associations and reproducibility of our findings, we have provided the complete list of 615,281 SNPs and their corresponding PIS values, along with the source code and example datasets in our Deep-Block GitHub repository (https://github.com/taehojo/Deep-Block/). The predictive performance analysis (Figure 4A) demonstrates that SNPs selected based on PIS values show increasing AUC scores, validating the utility of PIS rankings in variant identification. While traditional GWAS approaches rely on established *p*-value thresholds, our Deep-Block framework takes a more flexible approach, using known AD-associated variants as empirical benchmarks for significance assessment.

The eQTL analysis across brain regions revealed region-specific expression patterns. Our integrative approach showed that several variants had strong functional evidence. In particular, rs200986288 demonstrated widespread effects across brain regions (506 associations, average $\beta = 0.42$), while rs75997270 showed consistent upregulation ($p = 2.75\text{e-}40$, $\beta = 0.68$) across analyzed brain regions. These findings suggest potential functional roles beyond mere LD-based associations, though further functional analysis through fine-mapping and cross-population studies will be valuable for confirming the functionality. The cerebellar hemisphere showed 145 eQTL associations, cerebellum 131, and nucleus accumbens basal ganglia 124. Rs75997270, an intronic variant in *FRG1-DT* (lncRNA), had a significant association ($p = 2.75\text{e-}40$) in the nucleus accumbens and was detected across all analyzed brain regions. The *APOE* downstream

TABLE 2 SNPs with highest Phenotype Influence Scores (PIS) associated with AD

Rank	Feature	Chr.	Position	Variation	Gene	Importance	Reference
1	rs429358	19	44908683	T/C	*APOE*	8.00E-04	22
2	rs11556505	19	44892886	C/T	*TOMM40*	7.23E-04	24
3	rs34342646	19	44884872	G/A	*NECTIN2*	6.85E-04	25
4	rs5117	19	44915532	T/C	*APOC1*	6.85E-04	
5	rs483082	19	44912920	G/T	*APOC1*	6.09E-04	34
6	rs10414043	19	44912455	G/A	*APOC1*	5.43E-04	35
7	rs10119	19	44903415	G/A	*TOMM40*	5.11E-04	24
8	rs71352238	19	44891078	T/C	*TOMM40*	4.76E-04	35
9	rs6857	19	44888996	C/T	*NECTIN2*	4.63E-04	24
10	rs59007384	19	44893407	G/A G/T	*TOMM40*	4.57E-04	35
11	rs111789331	19	44923867	T/A		4.34E-04	
12	rs12721046	19	44917996	G/A	*APOC1*	3.75E-04	36
13	rs4420638	19	44919688	A/G	*APOC1*	3.61E-04	37
14	rs283811	19	44885242	A/C A/G	*NECTIN2*	3.37E-04	25
15	1:13243852	1	13243852	C/T		3.06E-04	
16	rs200986288	20	30185632	A/C A/T		2.87E-04	
17	rs199988716	2	95935492	G/A		2.51E-04	
18	rs202143966	9	63769614	T/C		2.49E-04	
19	rs377656811	22	16427107	C/A C/T		2.45E-04	
20	rs157582	19	44892961	C/T	*TOMM40*	2.37E-04	38
21	rs78790997	16	33736499	C/G	*LOC107984083*	2.28E-04	
22	rs141490255	1	58630472	G/A		2.27E-04	
23	rs75997270	4	189924739	C/A C/G	*LOC728339*	2.21E-04	
24	rs75627662	19	44910318	C/T		2.20E-04	
25	rs147747785	17	22046134	G/T		2.20E-04	
26	rs1160985	19	44900154	C/T	*TOMM40*	2.18E-04	39
27	rs2075650	19	44892361	A/G	*TOMM40*	2.16E-04	24
28	rs202221379	17	22046133	G/T		2.14E-04	
29	rs34404554	19	44892651	C/G	*TOMM40*	2.09E-04	35
30	rs769449	19	44906744	G/A	*APOE*	2.09E-04	40

Note: This table catalogs the top 30 SNPs ranked by PIS, derived from an extensive examination of 54,949 genetic variants within the top 1500 LD blocks using TabNet. The highest-scoring SNPs are predominantly located on chromosome 19, related to genes such as *APOE*, *APOC1*, *NECTIN2*, and *TOMM40*—well-established AD-associated genes. Additionally, this table includes novel findings, highlighting SNPs and genes previously unidentified in AD genetic association studies.

Abbreviations: AD, Alzheimer's disease; Chr., chromosome; SNPs, single nucleotide polymorphisms.

variant rs75627662 and *APOC1* intronic variant rs5117 were detected in the nucleus accumbens basal ganglia. rs200986288 was detected in 506 eQTL associations across the analyzed brain regions. The VEP and ANNOVAR analyses showed rs75627662 as an *APOE* downstream variant, rs5117 as an *APOC1* intronic variant, rs111789331 as an upstream variant of *APOC1P1*, and rs75997270 as an intronic variant within *FRG1-DT*.

The analysis also identified additional genetic variants and genes (e.g., rs199988716, *LOC107984083*, and *ANKRD30BL*) associated with AD. However, this study used sequencing data from NHW individuals, which may limit the broad applicability of the findings. As more ancestrally diverse cohorts become available in the ADSP, we look forward to extending these analyses to ensure broader relevance and applicability of findings across different populations.

5 | CONCLUSION

This study developed and applied the Deep-Block AI framework to large-scale ADSP WGS data for genetic association analysis for AD. The approach involved segmenting the whole genome into LD blocks and applying automated imputation of missing genotypes for data

preprocessing. The Deep-Block framework identified AD-associated genetic loci, including both previously identified and novel SNPs, supported by tissue-specific eQTL evidence across brain regions. The framework integrated eQTL analysis across brain regions and was compared with sliding window approaches in variant identification. Compared to traditional methods such as Plink and SKAT-O,[33] Deep-Block uses LD structure and attention-based feature selection to analyze high-dimensional genomic data more comprehensively, potentially capturing genetic interactions that are not detected by conventional approaches. Unlike SWAT-CNN,[10] which utilizes fixed genomic fragments, Deep-Block segments the genome based on LD-defined regions, thereby improving the identification of biologically relevant patterns. This framework demonstrates its capability to analyze large-scale genomic data effectively and identified both known and novel genetic variants associated with Alzheimer's disease.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

Consent from human subjects was not necessary for this study.

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SUPPORTING INFORMATION

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