Blood Gene Expression as a Biomarker for Alzheimer's Disease Detection: A Review

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Abstract--**Alzheimer's a type of neurological disorder is seeing a surge in the numbers of cases from the past decade. This paper focuses to explore and summarize the various feature selection and classifier algorithms that can make use of blood gene expression data and find the advantages of using blood gene expression data over other sources like MRI images and gene expression extracted from other tissues. We also aim to explore explainable artificial intelligence methods (XAI) of classification for a simple human interpretation and measure its trustworthiness.**

Keywords---Blood Gene Expression, Feature Selection, Explainable Artificial Intelligence

I. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the gradual loss of cognitive function and memory. It is the most common cause of dementia among older adults. Especially in India the cases are expected to grow to 11,422,692 by 2050 from 3,848,118 measured in 2019 according to Lancet report as of July 2022 [1]. The disease is caused by the accumulation of amyloid plaques and tau tangles in the brain, leading to the death of nerve cells and the disruption of communication between brain cells. As the disease progresses, individuals may have trouble with everyday tasks, behavioral changes, and eventually, complete dependence on caregivers. Despite intense research efforts, there is currently no cure for AD and available treatments only offer temporary symptom relief. Early detection and diagnosis of AD is crucial for the planning of appropriate care and support for individuals and their families, as well as for the development of disease-modifying therapies. However, current diagnostic methods for AD often involve invasive and expensive procedures, such as brain imaging or lumbar punctures. In recent years, there has been increasing interest in the use of blood-based biomarkers, such as gene expression patterns, as a less invasive and more cost-effective approach for the early detection of AD. The identification of specific gene expression patterns in the blood that are associated with AD may enable the development of simple and reliable diagnostic tools that can be used in a clinical setting.

Gene expression refers to the process by which the genetic information contained in DNA is used to synthesize the various proteins and other molecules that perform specific functions within cells. This process is regulated by a complex network of signaling pathways that control which genes are turned on or off in each cell at a given time. The measurement of gene expression, or transcriptomics, allows scientists to understand how cells respond to different stimuli and how they differ from one another. By analyzing gene expression data, researchers can gain insights into the underlying mechanisms of biological processes and diseases, such as cancer or Alzheimer's disease. Gene expression data can be obtained from a variety of sources, including tissues, cells, and biofluids such as blood. The use of blood-based gene expression data has the advantage of being non-invasive and easily accessible, making it a promising tool for the diagnosis and monitoring of diseases. In recent years, there has been growing interest in the use of gene expression data for the early detection and treatment of a wide range of conditions, including cancer, cardiovascular disease, and neurological disorders. The major problem that we must address while use blood gene expression data is the High Dimensionality of the dataset, since blood tissue can be used to extract around 10,000-30,000 genes on average and each of these genes might have 1-3 gene probes. DNA probes are usually single-stranded DNA molecules that are labeled with a detectable molecule, such as a fluorescent dye or a radioactive isotope. They are designed to bind to a complementary DNA sequence and are often used to detect the presence of specific genes or to analyze DNA modifications, such as methylation. RNA probes are like DNA probes, but they are designed to bind to complementary RNA sequences. They are often used to detect the presence and abundance of specific RNA molecules, such as mRNA or non-coding RNA. Protein probes are molecules that are designed to specifically bind to and detect the presence of a particular protein. They can be antibodies, small molecules, or other types of protein-binding molecules and are often used to analyze protein expression, localization, and function.

II. FEATURE SELECTION TECHINIQUES

High dimensionality poses a need for an efficient feature selection mechanism since the number of dimensions in a gene expression dataset would be close to 40,000. Feature selection techniques will allow us to design our classification models only based on the features that have a significant impact on exhibiting characteristics that can lead to development of AD.

A. Statistical Methods:

a. Significance Analysis on Microarrays (SAM): SAM is a statistical method used to identify genes or other features in a microarray dataset that are significantly different between two or more experimental conditions. Microarrays are a type of high-throughput technology used to measure the expression levels of thousands of genes or other biological features simultaneously. Genes with a low significance score are significantly differentially expressed, while genes with a high significance score are not considered to be significantly differentially expressed [18]. Lee, T et al. (2020) [2]: The authors have published a study on extracting differentially expressed genes (DEG) using SAM by taking use of three publicly available datasets ADNI, ANM1, ANM2. This involved comparing SAM with other state of the art feature selection algorithms like Least Absolute Shrinkage and Selection Operator (LASSO), Random Forest (RF). Before putting the data under the feature selection algorithms, the dataset was first filtered out to remove genes with expression value less than the median of the gene expression values in 100 samples and if a gene had multiple probes median of their values where used. This gave the authors around 21,698 unique genes to work with for feature selection. Among the various feature selection algorithm experimented Significance Analysis of Microarrays yielded the best results. Variable Auto Encoders were also used in this study but found to be not helpful in improving the performance when used along with the DEG found using SAM. Area Under the Curve (AUC) of 0.874 for ANM1 dataset was observed by the authors using ANM1 dataset

b. t-test: t-tests are used to determine whether there are statistically significant differences between the means of two groups. They are frequently employed to assess a novel therapy or strategy's efficacy. The t-test compares the magnitude of the difference between the two groups means to the variation within each group. The null hypothesis that there is no significant difference between the means can be rejected if the difference between the means is substantial relative to the variance within the groups. In this case, it is likely that the difference is not the result of chance. T-tests come in a variety of flavors, including paired, independent, and one-sample. Its application can be extended to Feature Selection to identify the important features when the given feature set is large. If the difference between the means of two groups (feature variable and output variable) is statistically significant then it suggests the importance of the feature in deciding the value of the output variable [19]. S. Khanal et al. (2021) [5]: have conducted the study using t-test between groups-of-interest. Based on their p-value results the groups are ordered to select top N genes. Group containing EMCI vs AD performed the best among the other groups, where accuracy (ACC) of 65% and AUC of 67% was observed. C. Park et al. (2020) [8]: conducted study using Limma package to extract DEG based on t-test. Conventional statistical methods were ignored as they could not reflect the biological process. GSE30000 and GSE44770 gene

expression from prefrontal cortex were integrated together and z-score normalized before putting for t-test to extract DEG. Since methylation played a major role in regulating gene DEG, gene expression datasets were integrated with DNA methylation dataset GSE80970 to identify Differentially Methylated Positions (DMP) using intersection operation performed between the gene expression sources. In k-fold cross validation, an avg. accuracy of 82.3% was observed when 35 gene extracted using t-test were used for classification.

c. Chi-square (χ^2): χ^2 is a statistical method used to determine where there is a statistically significant relation between observed frequency and expected frequency of a particular event. If the difference between the observed and expected values are differ by a large value, then we can reject the null hypothesis and state that the variables are related [20]. El-Gawady, A et al. (2022) [6]: have done the study on using χ^2 to extract the top 30 genes. This was employed along with 2 other statistical methods (ANOVA, MI) on a group 8 gene subsets created by integrating 4 genes expression datasets (GSE33000, GSE44770, GSE44768, GSE44771) extracted from different regions of the brain. The average of these metrics was used to order the genes and select the top 30 genes. Classification done using these 30 genes yielded a maximum ACC of 97.5% and AUC of 97.2%.

d. Analysis of Variance (ANOVA): ANOVA is a statistical method used to test if two groups of variables related by checking if there is a statistical difference between the mean s of the groups. This is a powerful tool which is now widely used in many fields including biology and psychology. It can be used with gene expression dataset to extracts genes having interested properties. El-Gawady, A et al. (2022) [6]: have done their research using ANOVA to extract the top 30 genes. This was employed along with 2 other statistical methods ($\chi2$, MI) on a group 8 gene subsets created by integrating 4 genes expression datasets (GSE33000, GSE44770, GSE44768, GSE44771) extracted from different regions of the brain. The average of these metrics was used to order the genes and select the top 30 genes. Classification done using these 30 genes yielded a maximum ACC of 97.5% and AUC of 97.2%. H. M. AL-Bermany et al. (2021) [9]: performed a study using ANOVA for feature selection along with other statistical methods. Threshold of p-value for the study was fixed as 0.05 and genes with less than this value were statistically significant and were added to the gene subset to be used for further processing by clustering techniques. ANOVA outperformed other statistical methods explored in the study and a maximum accuracy of 92.9% was observed.

e. Mutual Information (MI): MI is a statistical method used to identify the mutual dependence of two random variables. It can also be stated as the measure of

"Shared Information" between the two random variables. Larger the value of MI larger is the degree of dependency between the random variables. This is usually employed to state the usefulness of one variable over the other variable [21]. Hence this can be used with gene expression dataset to extract gene with required features. El-Gawady, A et al. (2022) [6]: have done their research using MI to extract the top 30 genes. This was employed along with 2 other statistical methods (χ^2, ANOVA) on a group 8 gene subsets created by integrating 4 genes expression datasets (GSE33000, GSE44770, GSE44768, GSE44771) extracted from different regions of the brain. The average of these metrics was used to order the genes and select the top 30 genes. Classification done using these 30 genes yielded a maximum ACC of 97.5% and AUC of 97.2%.

f. Principal Component Analysis (PCA): PCA is a statistical method that involves linear transformation of the given dataset into a new system where the sample can be represented with few dimensions. This technique aims to find the set principal components that exhibit maximum variance. Due to this PCA is used widely in genetic studies to find important gene sets from the given set of gene in the sample. S. Perera et al. (2020) [7]: conducted study in which PCA was used to select top 50 gene from 24,438 unique genes of samples from the data set GSE5281. PCA is found to be the most efficient way of feature selection among 2 other ensemble methods used in the study yielding a maximum ACC of 93.9% when 14 gene out of 50 top gene selected was used.

g. Least Absolute Shrinkage and Selection Operator (LASSO): LASSO is a variation of linear regression model that is used to select important features and shrinking the less important features. The shrinkage factor is controlled by the penalty that is assigned to each of the features. As the value of the penalty increase the value of parameter is shrunken more towards zero [23]. A. Sharma et al. (2021) [10]: conducted study in which LASSO was used along with other Random Forest based feature selection techniques. Data from 4 regions of brain (Prefrontal Cortex, Medial temporal gyrus, Hippocampus, Entorhinal cortex) were integrated and batch normalized using z-test. In the study R package "caret" was used to implement LASSO. Study results showed standalone LASSO feature selected performed well in classification of AD in 3 brain regions Prefrontal Cortex, Medial temporal gyrus, Entorhinal cortex with ACC of 100%, 99% and 98% respectively. Kalkan H et al. (2022) [11]: proposed a method to LASSO for feature selection from gene expression datasets GSE63060, GSE63061 and GSE140829. A total of 488 unique gene symbols were identified which were converted into a 2D image using Linear Discriminant Analysis (LDA). A maximum ACC of 84.2% was observed when classification was done using this 2D image representation.

B. Ensemble Methods:

a. Adaptive Boosting (Adaboost): Adaboost technique is an Ensemble method using decision trees. These uses set of weak learners for fast implementation and to converge faster into the results and doesn't require any prior domain knowledge in creating the weak learners. The goal of the weak leaners is to identify the weak hypothesis. Mahendran N et al. (2022) [4]: have conducted their study on Adaboost to find 12 differentially methylated that are most significant in identifying the AD. Out of these 6 were hypo-methylated and the other 6 were hyper-methylated. These 12 identified genes were k-fold validated using Logistic Regression (LR) model and a validation accuracy of 87.1% was observed when k = 3. The genes associated with these positions were MS4A4, MYNN, TXNIP, CORO2B, NOG, BEX2, PIGA, FAM82A1 and CDKN1C.

b. Random Forest (RF): RF is a most popular ensemble technique which is used for task such as classification and regression. From the give sample of dataset random sub samples are generated for each of which a classifier is modelled. The classifiers are then ensembled together to make the final classification. This technique can be used to extract the import feature by using a metric called as feature importance. For a feature this metric is found by identifying how much role it plays in its respective decisions trees classification accuracy. S. Perera et al. (2020) [7]: The authors conducted the study using RF on dataset GSE5281. This dataset contained a total on 161 samples with 24,438 unique gene symbols. RF was studied along with 2 other feature selection technique to extract the top 50 features based on their feature importance scores and PCA was found to outperform the RF feature selection technique. D. Sun et al. (2022) [12]: conducted study with dataset from 4 sources viz. GSE5281, GSE44771, GSE109887 and GSE132903 were GSE5281, GSE44771 were combined to increase sample size and GSE109887, GSE132903 were used for validation. Using Gene Ontology and Pathway Enrichment top 120 genes where extracted. These 120 genes were reduced further to 6 gene symbols using RF. A maximum average ACC of 92.3% was observed when model validated using 5-fold cross validation.

c. Variable Selection using Random Forest (varSelRF): varSelRF is a variation of Random Forest technique which is an ensemble method using decision tree. This technique is well suited for regression, classification and feature selection task. varSelRF involves building of decision trees and selection the nodes or features that are widely available across multiple trees. Nodes present in the top of the tree are the most important features. varSelRF is robust in identifying both linear and non-linear relationships between features. A. Sharma et al. (2021) [10]: conducted study using varSelRF along with LASSO to select important

genes for classification of AD using gene expression dataset extracted form 4 different brain regions (Prefrontal Cortex, Medial temporal gyrus, Hippocampus, Entorhinal cortex). Genes selected from only varSelRF performed well in 3 regions Prefrontal Cortex, Hippocampus, Entorhinal cortex with ACC of 95%, 94% and 95% respectively. However, a max ACC of 98% was observed when the features selected using LASSO were integrated with features selected using varSelRF.

d. Extra Tree Classifier (ETC): ETC is a similar technique to RF. The way in which ETC uses a random threshold for each feature in the dataset when constructing the nodes of the decision tree is what makes it different from RF. This level of randomization helps the ETC to be more reliable in reducing the noise and to avoid overfitting. S. Perera et al. (2020) [7]: The authors conducted the study on ETC using dataset GSE5281 which contained a total on 161 samples with 24,438 unique gene symbols. ETC was compared with 2 other feature selection technique to extract the top 50 features based on their feature importance score and PCA was found to outperform the ETC.

e. Adaptive Boosting for miRNA Disease Association (ABMDA): Ensemble based technique specifically designed to locate differentially expression miRNA (DEmiRNAs). Uses the augmentation of meta-analysis to identify specific RNA sites responsible for a disease under consideration. Yuen, S.C (2021) [13]: used ABMDA to extract 28 DEmiRNA which were the potential biomarkers for classification of AD. However, these 28 DEmiRNAs identified in the study were not put of classification using conventional classification methods instead were cross validated using biological pathway analysis.

C. Others:

a. Variational Autoencoders (VAEs): It is a generative model used to recognize the features, trends and distribution in the given sample. VAEs can be used thereby to find a compacted or an encoded version of the given dataset which helps in reducing the dimension of the given dataset while preserving the important features. VAEs have 2 components called Encoder and Decoder. Encoder phase of the model is used to find a compacted representation of the input sample and Decoder phase is used to reconstruct the actual sample from the compacted input representation. The loss function is the difference between the reconstructed sample and the actual sample which is then used in backpropagation to fine tune the encoder phase. Lee, T et al. (2020) [2]: have conducted study on using VAEs to reduce the dimension of the samples collected as part of datasets ADNI, ANM1, ANM2. VAEs was used to construct a compacted version of DEG which was then used for classification phase. Study found SAM feature

selection technique outperformed DEG+VAEs technique as it was found VAEs seemed to lose important features in encoding gene expression values responsible for AD.

III. CLASSIFICATION TECHNIQUES

With the extracted genes classification techniques are used to distinguish between healthy control samples (CN) from samples collected from people with AD or mild cognitive impairment (MCI). The choice of feature selection algorithms was seen to affect the ability of the classification model due to the high dimensionality problem.

A. Support Vector Machine (SVM): SVM is the most popular and widely used linear classifier technique. This involves classification based on supervised learning approach. Lee, T et al. (2020) [2]: The authors conducted the study on SVM along with various classification models like LR, L1 regularized LR (L1-LR), Deep Neural Network (DNN), RF. SVM was observed to be well paired with SAM feature selection algorithm. AUC of 0.874 was observed in the ANM1 dataset which was significantly higher when SVM was used with other feature selection algorithms like VAE as authors found VAE lost critical information's while reducing the dimensions. Kamal et al. (2021) [3]: This study also used SVM for classification for their multi-model diagnostic system and found it to outperform k-nearest and Xboost techniques. Accuracy of 82.4% with Precession of 81.8% was observed indicating the advantage of using it against a high dimensional dataset. El-Gawady, A et al. (2022) [6]: have conducted study by using SVM for classification of AD over the 30 genes extracted using the statistical methods ($\chi2$, ANOVA, MI). SVM was used along with other classification methods like RF, LR, AdaBoost and SVM was found to outperform these techniques. Maximum ACC of 97.5% and AUC of 97.2% for the set having pairwise intersection of 4 datasets (GSE33000, GSE44770, GSE44768, GSE44771) was observed for the study. As the datasets uses tissues collected from brain this would be only possible with autopsy or biopsy which is less feasible when compared to gene expression collected from other tissues like blood. S. Perera et al. (2020) [7]: conducted their study involving SVM as their classification technique and found to be yielding a maximum ACC of 93.9% when evaluated using top 14 genes collected using PCA technique. SVM with Linear Kernel in the study was found to outperform other techniques such as SVM with Gaussian Kernel and RF used in the study.

B. K-Nearest Neighbors (KNN): Kamal et al. (2021) [3]: The authors have conducted a study on KNN by designing a multi-model diagnostic system using a combination of classifiers that use MRI images as well as gene expression data. The study is focused on reducing the computational time as previous research were focused on the use of complex DNN and feature selection techniques. Using GSE174367 dataset classifier techniques such as KNN, SVM, Xboost are

explored. KNN a classifier which determines the class level based on the Euclidean distance was found to not perform well due to the input having very large dimension. H. M. AL-Bermany et al. (2021) [9]: used KNN along with Deep Neural Network for performing classification task on the gene subset extracted using ANOVA and MI. In this study KNN was used to organize genes as clusters having same data points. From the given D genes in the data K genes were extracted, where K < D is strictly maintained. ANOVA was found to work to pair well with ANOVA than MI were a maximum accuracy of 92.9% was observed.

C. Convolution Neural Network (CNN): A common deep learning model predominantly used for classification tasks, such as image classification, image segmentation and object detection. Has special layers called convolution layers which perform mathematical operation called convolution on the input data based on a kernel with static size. CNN models also use polling layers to down sample or to reduce dimension using min, max or average of the values over a small region. Though CNN are mainly designed for image classification this can be extended to classification of AD using gene expression as biomarker. H. M. AL-Bermany et al. (2021) [9]: used CNN for classification of AD using the gene clusters extracted using KNN. CNN's performance was evaluated without using KNN as well and found CNN performed better when gene clustering with KNN was carried out. ACC of 92.9% was observed when ANOVA for feature selection, KNN for feature clustering and CNN for classification was used. Kalkan H et al. (2022) [11]: study used CNN for classifying dataset formed by integration 3 datasets GSE63060, GSE63061 and GSE140829. The integrated datasets where Min-Max normalized to rescale the RNA expression values between 0 and 1. Gene other the common genes across all the three datasets were ignored resulting in 11,618 unique genes. A total of 488 important genes were selected using feature selection technique involving LASSO. LDA was employed to map the 488 into a 2D space which is a supervised learning model separating the dataset into groups or classes to improve the accuracy of the classification model. The extracted image was then passed to the CNN model with 6 convolution layers, 3 max pooling layers and 2 Dense layers. A maximum ACC of 84.2% was observed.

D. Deep Neural Network (DNN): DNNs with output layers having SoftMax activation functions are generally used for designing classification models. The number of layers, nodes at each layer, activation and loss functions are each layer depend on the domain over which classification is applied. DNN models with classification done using gene expression values with large dimensions require model to be complex with large number of hidden layers. If number of unique gene are fewer complex models lead to overfitting. C. Park et al. (2020) [8]: conducted study using DNN to perform classification with the 35 genes extracted using the t-test. The study proposed the DNN model with 8 layers, 306 nodes with dropout 0.85 and Learning rate of 0.02 and

observed in k-fold cross validation an avg. accuracy of 82.3%. When compared to other classification techniques such as RF, SVM and Naïve Bayesian the proposed DNN model performed better in the study. D. Sun et al. (2022) [12]: used DNN in their study to classify AD using 6 genes extracted using RF based feature selection technique. The model was built using 6 input layers, 5 hidden layers and 2 output layers. An average accuracy of 92.3% was observed when model was put on 5-fold cross validation.

E. Deep Recurrent Neural Network (DRNN): This is a special kind of muti-layer neural network in which output of one layer is again fed as input to the layer. This acts as a memory which carries necessary information about the previous states. This is different from the usual neural network as in typical network the input and output neurons are completely independent of each other. Mahendran N et al. (2022) [4]: have conducted study on DRNN and have proposed an enhanced version called Enhanced DRNN (EDRNN). The selected genes from the Ada Boost feature selection technique are provided as input to these models in their study. EDRNN was implement with early stopping criteria to avoid overfitting and had considerable depth in the hidden layers of the output area for better accuracy. This model in their study was compared against state-of-the-art approaches like RNN and CNN. The accuracy of 89.4% showed it outperformed the existing systems.

F. eXtreme Gradient Boosting (XGBoost): XGBoost is an ensemble based boosting algorithm in which multiple weak decision trees are ensembled together into a single strong model. Advantage of XGBoost is that it allows to dynamically adapt the hyperparameters like maximum depth of trees and learning rate. S. Khanal et al. [2021]: have conducted the study on using XGBoost on dataset after the feature set are filtered using 2-step feature selection techniques t-test and SelectFromFeature. A maximum ACC of 65% and AUC of 67% for the gene group EMCI vs AD was observed.

G. Elastic Net (ElasticN): ElasticN model is obtained when L1 (Lasso) and L2 (Ridge) regularized linear regression models are combined. The dominance of L1 and L2 is controlled by a parameter called alpha, where alpha = 1 then it corresponds to Lasso and when alpha = 0 it is Ridge. This model has known to have a great immunity against overfitting by shrinking the less important features close to 0 as much as possible. ElasticN has the capability to handle large and correlated features better than other classification models. A. Sharma et al. (2021) [10]: conducted the study using the ElasticN with top 208 genes selected using LASSO and varSelRF from the gene expression collected from 4 difference brain regions (Prefrontal Cortex, Medial temporal gyrus, Hippocampus, Entorhinal cortex). ElasticN was found to perform well in all the 4 brain regions compared to other classification models such as SVM and RF. An average ACC of 98% was observed in the study.

IV. DISCUSSION

In this study, we aimed to identify the most effective feature selection and classification methods for the classification of AD using gene expression data. High dimensionality is a common problem in gene expression data, and feature selection techniques are needed to effectively analyze the data and identify potential biomarkers for AD. We evaluated several feature selection methods on multiple categories, including Statistical methods, Ensemble Learning methods and other miscellaneous methods. Table 1 summarizes the study on various feature selection and classification techniques that have been explored. Study was also aimed to explore the advantages of using blood gene expression as biomarker instead of currently widely used methods using MRI images.

Gene expression data from different brain regions was observed to perform better than the gene expression extracted from blood tissues. A max ACC of 98% and 97.2% was observed as per the study A. Sharma et al. [10] and El-Gawady, A et al. [6] respectively. However, extracting gene expression from brain tissues would involve autopsy or biopsy which are invasive and less feasible when compared to extracting gene expression from blood tissues. A max ACC of 92.9% was observed in the study conducted by H. M. AL-Bermany et al. [9] indicating gene expression is feasible and accurate for AD classification.

Study	Dataset Used	Feature Selection Alg.	No. of Genes	Classification Alg.	Performance
Lee, T et al.	GSE3060 GSE3061	SAM	697	SVM	AUC: 87.4%
M. S. Kamal et al.	GSE174367	-	18,234	KNN SVM	ACC: 64.5% ACC: 82.4%
Mahendran, N et al.	GSE76105	Adaboost	12	DRNN	ACC: 89.4%
S. Khanal et al.	ADNI	t-test + SelectFromFeature	25	XGBoost	ACC: 65% AUC: 67%
El-Gawady, A et al.	GSE33000 GSE44770 GSE44768 GSE44771	χ^2, ANOVA, MI	30	SVM	ACC: 97.5% AUC: 97.2%
S. Perera et al.	GSE5281	PCA, RF, ETC	14	SVM	ACC: 93.9%
C. Park et al.	GSE33000 GSE44770 GSE80970	t-test	35	DNN	ACC: 82.3%
H. M. AL-Bermany et al.	GSE3060 GSE3061	ANOVA + k-means	2500	CNN	ACC: 92.9%
A. Sharma et al.	GSE33000 GSE44770 GSE118553 GSE1132903 GSE5281 GSE48350 GSE28146 GSE5281 GSE48350 GSE4757	varSelRF + LASSO	208	ElasticN	ACC: 0.98
Kalkan H et al.	GSE63060 GSE63061 GSE140829	LASSO	488	CNN	ACC: 84.2% AUC: 87.5%
D. Sun et al.	GSE5281 GSE44771 GSE109887 GSE132903	RF	6	DNN	ACC: 92.3%

Table 1: Summary of studies conducted on detection of AD using various feature selection and classification techniques with gene expression.

Statistical methods such as SAM, t-test, χ^2, ANOVA, MI, PCA and LASSO methods were observed to be simpler to implement and most effective in understanding the correlation between features. Out of all the statistical methods studied χ^2 was observed to perform well when used as a standalone feature selection method with max ACC of 97.2% with gene expression data extracted from bran tissues extracted from different region of the brain. Ensemble methods such as RF, ETC, Adaboost, and varSelRF were also explored and were also found to be effective in the removing the dominance of irrelevant features from the

input feature set. Multiple decision trees were ensemble together in these approaches to rank nodes based on their importance in the classification of AD. As per existing study maximum ACC of 95% was observed when ensemble method varSelRF. However, when Ensemble and Statistical methods were combined as per done in study A. Sharma et al. [10] a significant improvement in the accuracy was observed. Since the important features left out by one method is caught by the other the combination proved to be the most suitable way for feature selection. Combination of varSelRF and LASSO yielded a max average accuracy of 98% on the datasets extracted from different brain regions.

Multiple state-of-the-art classification techniques such as DNN, CNN, SVM, KNN, ElasticN, DRNN were also evaluated. With reference to the study done by M. S. Kamal et al. [3] from the results it was observed ACC of classification model was heavily influenced by the efficiency and accuracy of the feature selection technique. Use of high dimensional genes directly without reducing the dimensions for classification yielded ACC of just 82.4% from which we can concluded that feature selection plays an important role in reducing the problem on overfitting by the classification models. SVM was found to be the most popular and widely used linear classifier technique for the classification of AD. However, ElasticN was observed to be the top performing model with max ACC of 98% when used for classification with genes selected from varSelRF and LASSO.

In this study AD classification techniques that does not depend on gene expression data were also explored to prove the advantages of using blood gene expression as biomarker. Table 2 summarizes the studies that rely on other sources for AD classification such as MRI images. S. Pavalarajan et al. (2022): conducted the study to classify AD patients using their MRI images. Proposed model in the study was trained using MRI images from OASIS dataset. Preprocessing task such as handling missing data, feature scaling and test train split was carried out before classifying the image set using classification techniques such as RF, LR, SVM and Decision Tree. RF performed better compared to other models with a max ACC of 83.5%. S. S. Rajeswari et al. (2021) [15]: performed study using MRI images collected as part public repository ADNI. Transfer Learning was used in the study to achieve high accuracy and to overcome the large dataset constraint since to improve the accuracy of the classification model image with high resolution was used. For classification of AD state-of-the-art models such as VGG-16, VGG-19 and Resnet-50 were used. Compared to other models VGG-19 yielded better accuracy of 98%. VGG-19 model was modelled with 16 3x3 convolution layers, 5 2x2 max-pooling layers and 3 fully connected layers. J. Li et al. (2022) [16]: performed the study using 3-D brain T1-weighted structure MRI images from ADNI public source. Data preprocessing methods such as resampling, skull stripping, intensity correction and clipping were explored. U-Net CNN is a variation of vanilla CNN which was found to perform better with the 3-D MRI images. S. Basheer et al. (2021) [17]: performed study on OASIS dataset of MRI images where classification was done using CapNet. CapNet was implemented using MCapNet package in python. A max ACC of 92.39% was observed and the proposed model was observed to outperform other conventional classification methods such as CNN. Hence, as the accuracy of models using gene expression as biomarkers have accuracy closer or sometimes better compared to existing systems using MRI images, blood gene expression can be seen as an effective biomarker for AD classification.

Study	Dataset	Classification Alg.	Accuracy
S. Pavalarajan et al.	OASIS	RF	ACC: 83.50%
S. S. Rajeswari et al.	ADNI	VGG-19	ACC: 98.00%
J. Li et al.	ADNI	3-D U-Net CNN	ACC: 95.06%
S. Basheer et al.	OASIS	CapNet	ACC: 92.39%

Table 2: Summary of studies using datasets other than gene expression

V. CONCLUSION

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