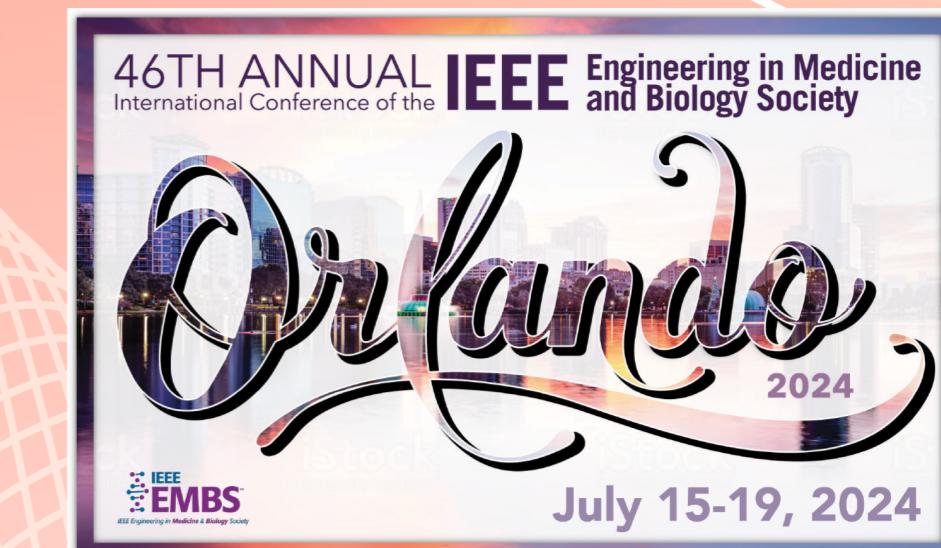


# Predicting csf A- $\beta$ /Tau Ratios for Alzheimer's Disease Diagnosis using Blood Gene Expression

Emine Güven<sup>1\*</sup>, Andrea Pearson<sup>1</sup>, James Lah<sup>2</sup>, Roger P. Simon<sup>1</sup>, Robert Meller<sup>1</sup>



<sup>1</sup>Neuroscience Institute, Morehouse School of Medicine, <sup>2</sup>Alzheimers Disease Research Center, Emory University.

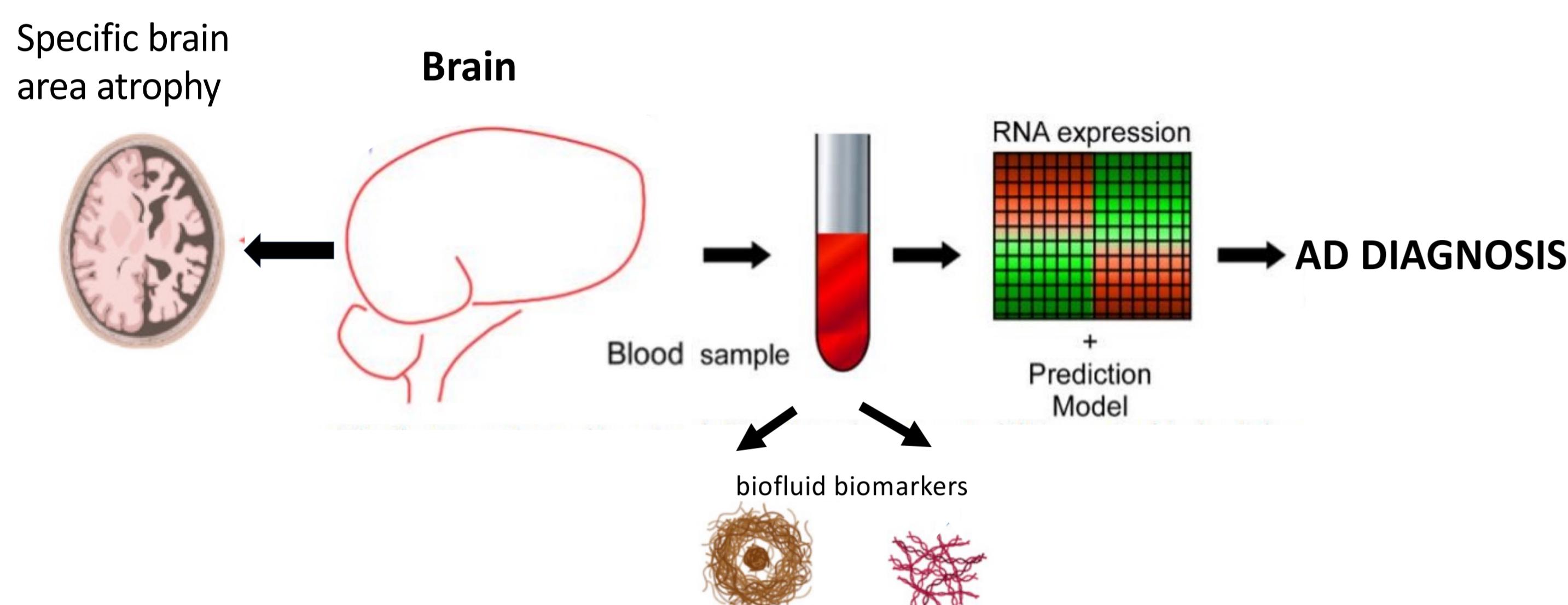
\*E-mail:eguven@msm.edu

## INTRODUCTION

- Alzheimer's disease (AD) is a complex neurodegenerative condition influenced by a combination of genetic, biological, and environmental factors.
- AD presents a significant challenge in both diagnosis and prognosis, particularly in distinguishing it from other forms of dementia and identifying patients with mild cognitive impairment (MCI) likely to progress to AD.
- We evaluated the accuracy of blood RNA expression profiles to predict AD diagnosis (csf A- $\beta$ /Tau ratios) in early onset AD diagnosis and age-matched healthy patients.

## OBJECTIVES

- The current biomarker used to stage an AD diagnosis, measurement of Beta Amyloid, Tau and phosphorylated tau proteins in cerebrospinal fluid (CSF).
- Here (Fig 1), we investigate the utility of blood transcriptomics to predict the A- $\beta$ /Tau ratio as an alternative diagnostic assay which is more convenient than lumbar puncture (LP).

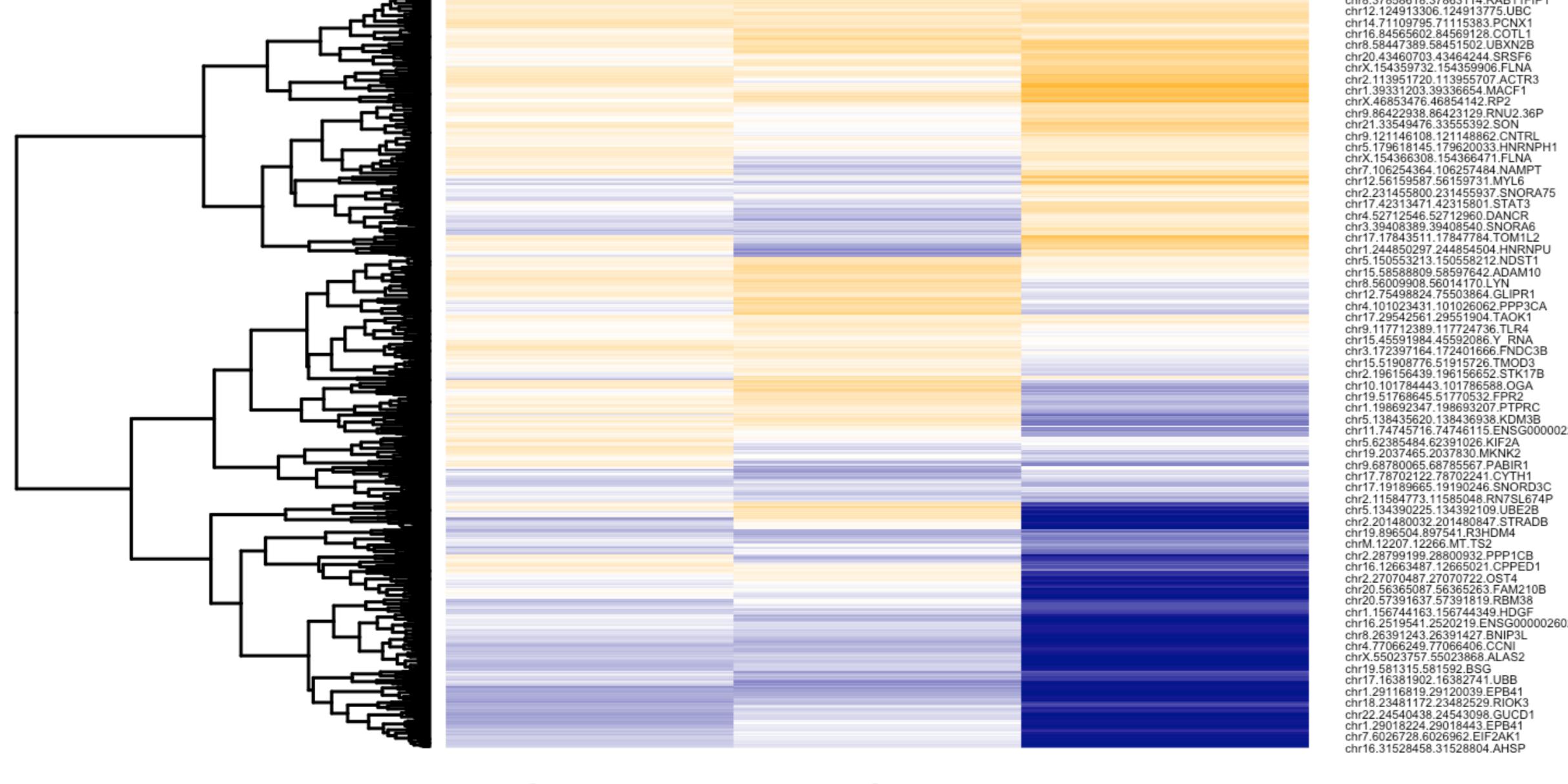


**Fig 1:** Overview of the study. Workflow to determine the utility of blood RNA profiles for retrospective AD detection.

## RESULTS

### Weighted Exon Co-expression Analysis Reveals exon networks correlating to A- $\beta$ /Tau status which change as the disease progresses

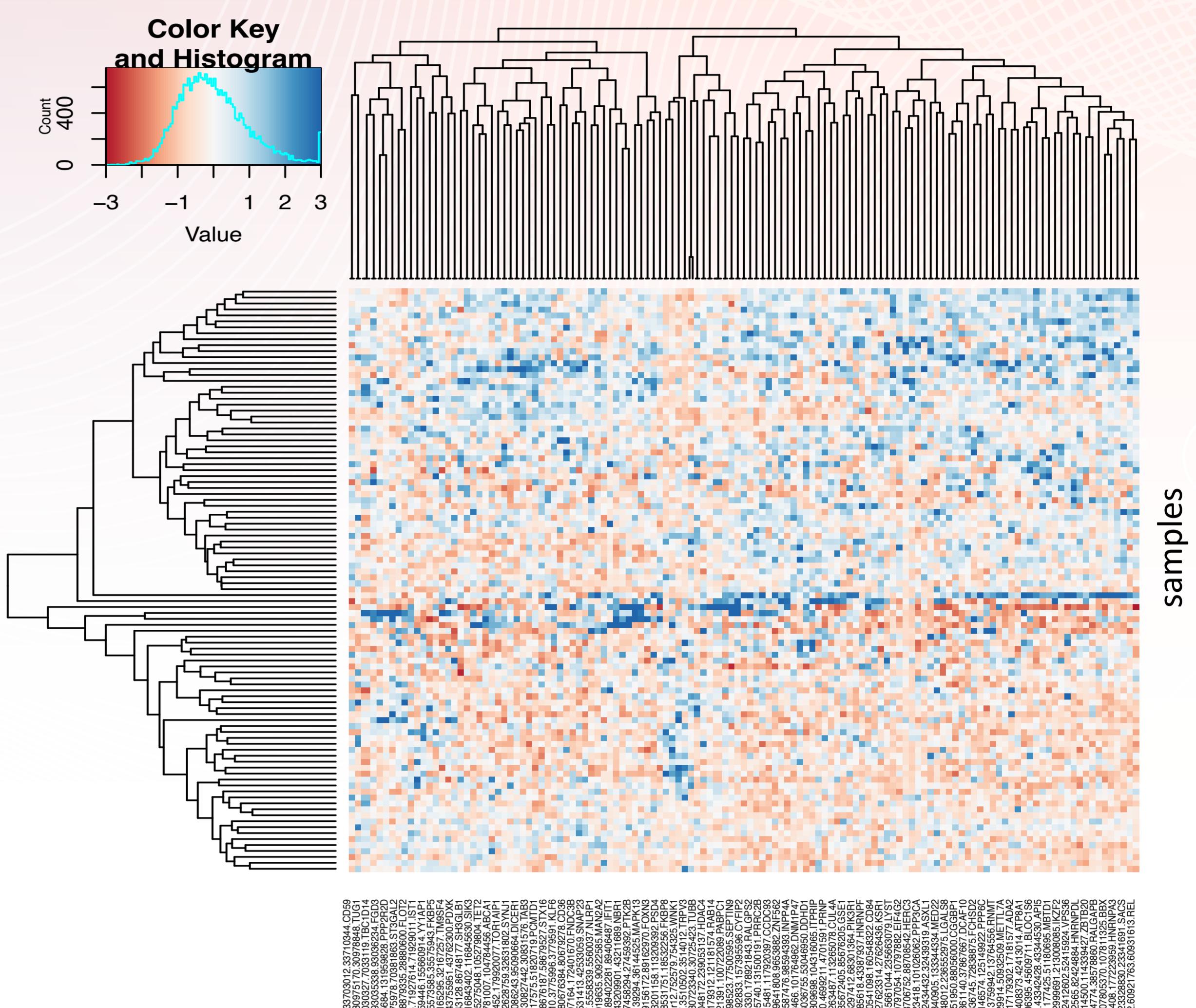
RNA-seq data from 122 patients (24-AD, 40-MCI, 58-Control) were subjected to WGCNA analysis. Exon expression data were subjected to correlation, and gene modules correlated to A- $\beta$ /Tau ratios. Gene expression values from each module were then grouped by clinical status, as shown in Fig 2.



**Fig 2:** Each subject modules of common genes tested for correlation with the A- $\beta$  /Tau ratios. Cell colors encode correlation coefficients (orange, positive correlation; purple, negative correlation). Color scale indicates the range of correlation coefficients. Data are grouped by clinical disease progression.

## Correlation matrix to filter featured genes

From the WGCNA analysis, we subset the control and MCI data and reduced our dataset dimension using a "spearman" correlation vs A- $\beta$ /Tau ratio ( $R^2 > 0.99$ ) (Fig. 3).



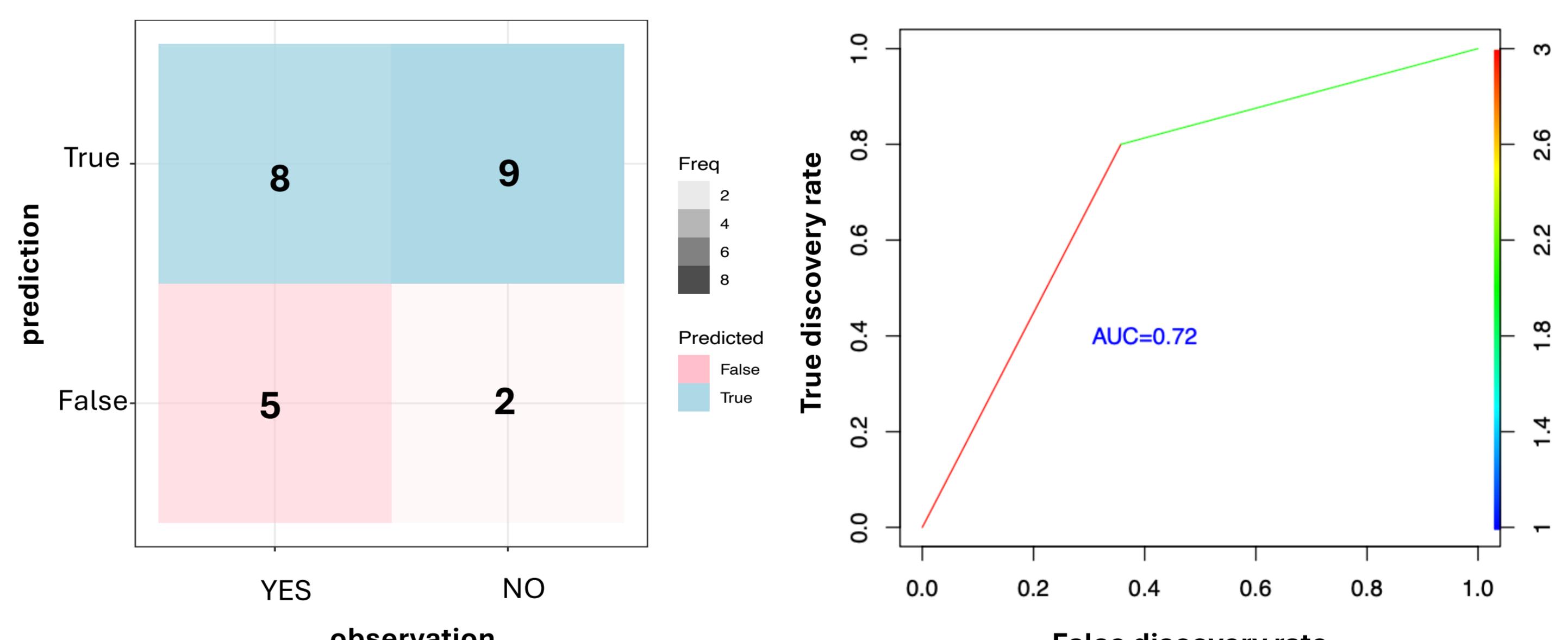
**Fig 3:** The heatmap of the highly correlated 254 genes and 98 sample.

## Predicting AD biomarker status using Naïve Bayes ML Model

- A- $\beta$ /Tau ratios were converted to binomial "YES" and "NO" ( using a cut-off ratio  $< 5.64$ ) according to suggestion of clinicians.
- The training set was randomly chosen from 58 samples out of 98 samples and subjected to **Naïve Bayes**, **glm**, **rpart**, and **svm** modeling, with 10-fold cross-validation.
- All models predicted the training data with an Accuracy = 1.
- **Naive Bayes** model, presented the highest prediction accuracy among the testing data set, 17 samples out of 24 samples are predicted correctly with an accuracy = 0.71 and error = 0.29 (sensitivity = 0.64, specificity = 0.80)

Fig 4.

## Confusion Matrix and ROC Analysis of the Prediction



**Fig 4: (Right)** Confusion Matrix showing performance of NB prediction model on testing datasets. Predictive class memberships **TP = 9**, **TN = 8**, **FP = 2**, **FN = 5**. **(Left)** ROC analysis result reported as **AUC = 0.72** with a **TPR = 0.64** and **FPR= 0.80**.

## CONCLUSIONS

The Naïve Bayes model was applied to a validation group of 24 patients, consisting of 15 control individuals and 9 individuals with mild cognitive impairment (MCI). The model showed potential but needs improvement, with 2 false positives and 5 false negatives in predicting control among 24 patients, indicating accurate control detection.

## REFERENCES

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