Aspects of Molecular Medicine 5 (2025) 100070

Contents lists available at ScienceDirect

Aspects of Molecular Medicine

journal homepage: www.journals.elsevier.com/aspects-of-molecular-medicine

Computational framework for analyzing miRNA-mRNA interactions in sarcopenia: Insights into age-related muscular degeneration

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ARTICLE INFO

Handling Editor: Prof A Angelo Azzi

Keywords:
Sarcopenia
miR-186–5p
Differentially expressed genes (DEGs)
miRNA-mRNA interactions
Transcriptomic analysis

ABSTRACT

Background: Sarcopenia, an age-related loss of skeletal muscle mass and function, impairs mobility, fragility, and quality of life. Despite progress in pathophysiology, molecular processes remain unknown. Recent research has investigated miRNAs as biomarkers for sarcopenia diagnosis and therapy. This work analyses differentially expressed genes (DEGs) and predicts miRNA-mRNA interactions using ML methods like XG-Boost and SHAP to find biomarkers.

Objective: This work evaluated the function of miRNA-mRNA interactions in sarcopenia pathogenesis and identified possible biomarkers by transcriptome analysis utilizing machine learning.

Methods: High-throughput mRNA sequencing datasets (GSE111006, GSE111010, and GSE111016) from GEO database were combined, pre-processed, and normalized using TPM and DESeq2 methods. XG-Boost regression analysis used 80/20 training and testing sets. SHAP analysis was used to evaluate model data and find significant DEGs. PPI networks were created using the STRING database, while miRNA-mRNA interactions were predicted using Encori and displayed with Cytoscape. The degree scores of miRNA-mRNA interactions were utilized to find biomarkers.

Results: XG-Boost and SHAP analysis revealed 20 influential DEGs linked to sarcopenia. With 97% accuracy, the model predicted accurately. PPI network research identified six hub genes: NTRK2, PCK1, DSP, SCD, MMRN1, and EDIL3. MiRNA-mRNA interaction analysis found miR-186–5p as the highest-degree biomarker candidate (36). MiR-186–5p was linked to muscle metabolism, hypertrophy, and exercise response.

Conclusion: The study found miR-186–5p to be a promising biomarker for sarcopenia using an integrated machine learning technique. The findings show that miR-186–5p may be a diagnostic and therapeutic target for sarcopenia, revealing its pathogenesis and enabling tailored treatments. Experimental research is needed to prove its therapeutic value.

1. Introduction

Sarcopenia is a term that comes from the Greek phrase “poverty of flesh." Age-related loss of lean body mass that impairs independence, mobility, and nutritional health was initially defined as it in the 1980s (Rosenberg, 1997). The definition of sarcopenia is an accelerated loss of muscle mass and function associated with a progressive, generalized skeletal muscle disease. Morbidity falls, frailty and functional decline are among the more unfavorable outcomes linked to sarcopenia (Cruz-Jentoft et al., 2018). Initially, “sarcopenia" was used to refer to muscle wasting (poor muscle mass) without considering functionality in certain scientific investigations on cancer and other disorders. It reduces quality of life and causes weakness and disability. Sarcopenia management and treatment depend on early diagnosis (Cooper et al., 2010, 2011; Dodds et al., 2016). Measurements of muscular mass, muscular strength, and physical performance are traditionally needed to diagnose sarcopenia. Every definition uses two or more factors, but how these definitions are applied in clinical practice varies, making

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https://doi.org/10.1016/j.amolm.2025.100070
Received 30 December 2024; Received in revised form 24 February 2025; Accepted 3 March 2025
Available online 7 March 2025

standardization difficult (Beaudart et al., 2019). To address this, the Asian Working Group for Sarcopenia (AWGSOP) and European Working Group on Sarcopenia in Older People (EWGSOP) have developed diagnostic criteria. Sarcopenia diagnosis requires muscle mass assessment. CT, MRI, and DEXA measure muscle mass. If diagnostic results vary by instrument and are not widely available in primary care, it might be difficult to identify at-risk sarcopenia patients and follow therapy management. Multiple sarcopenia diagnoses include malnutrition, cachexia, and frailty. (Jeejeebhoy, 2012; Ter Beek et al., 2016; Thomas, 2007). Recent advances in sarcopenia diagnosis include machine learning algorithms. Sarcopenia can be diagnosed and treated early using these better models. Quality of life increases and healthcare system pressure decreases. Thorough research examined how language affects sarcopenia in older adults. The examination highlighted the highest pooled prevalence estimates. (40·4% [19·5–61·2]) were from older definitions that simply employed assessment of muscle mass, whereas the very first 2010 EWGSOP definition produced one of the least pooled prevalence estimates (12·9% [95% CI 9·9–15·5] (Mayhew et al., 2019). Cutoff points for muscle mass have a greater impact on prevalence estimates than do cutoff points for muscle function (Masanés et al., 2017) (Ashraf et al., 2024).

The transcriptome and proteome techniques have characterized several components contributing to sarcopenia (Hwang et al., 2014). However, the molecular processes of aging-related skeletal muscle changes are unknown. The gene product microRNA can impede mRNA translation. As master mediators, miRNAs govern hundreds of target mRNAs to regulate cellular processes including proliferation, death, and development. Also, miRNAs may be useful targets for therapy and diagnostics in several illnesses (Gao and Jiang, 2016).Elevated concentrations of certain miRNAs have been linked to muscle pathology and cardiovascular disease by blocking protein synthesis (Bhat et al., 2024; Cordani et al., 2024; Nguyen et al., 2021; Ochoa et al., 2016). Despite medical and technological advances, the cause of sarcopenia is unknown. Machine learning (ML) algorithms predict outcomes by finding correlations between patient features and outcomes using statistical methods on huge datasets. Machine learning is used in medical image/video processing, biomarker discovery, diagnosis, class estimation, and therapy. Machine learning utilizes several approaches, some well-known. These include Gaussian process RBF, Decision Tree, Random Forest, AdaBoost, Gaussian Naive Bayes, Nearest Neighbors, Linear SVM, Radial Basis Function (RBF) SVM, and others. Still, there is no proven paradigm that works across all databases. XG-Boost and SHAP, sophisticated machine learning techniques, were used to evaluate high-throughput mRNA sequencing datasets and uncover sarcopenia-associated DEGs. XG-Boost predicted genes precisely, whereas SHAP showed how specific characteristics affected the model's output to predict expressed genes and create miRNA-mRNA to predict sarcopenia biomarkers.

2. Materials and methods

2.1. Preparation of dataset

High throughput analysis of mRNAs sequencing data of skeletal muscle transcriptome profiling was obtained from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). Totally 3 series of studies were obtained for the analysis, including GSE111006, GSE111010, and GSE111016 low muscle mass with or without sarcopenia. Additionally, repeated or duplicated genes were deleted for further analysis. The 3 data series were combined to form a single dataset for analysis. The Anaconda navigator tool of Jupyter Notebook was used for XG-Boost and SHAP analysis. Further, the combined dataset was preprocessed to handle the missing values and encode the variables. Machine learning was the subset of artificial intelligence such as SHAP (SHapley Additive exPlanations) and XG-Boost was employed to analyze the dataset. This helps in the development of a predictive model for a large number of datasets.

2.2. Data processing

After merging and preprocessing the mRNA sequencing data from GSE111006, GSE111010, and GSE111016, duplicates were removed and missing values were imputed using k-nearest neighbors (KNN). The TPM technique was used for normalization, while DESeq2 was used for differential expression analysis during feature selection. The dataset was divided into test and training sets of 80/20 split for machine learning by using SHAP and XG-Boost. The genes are processed based on the LogFC and P, Value of the dataset.

2.3. XG-boost and SHAP

The combined dataset of mRNA was processed by the regression analysis by using XGBoost (XGBRegressor with objective = 'reg:squarederror' and eval_metric = 'rmse') to build the predictive model. SHAP was used to interpret the values which were obtained from the XG-Boost model which helps in highlighting the impact of each feature to predict and identify potential genes of sarcopenia.

2.4. Data analysis

Metrics like as accuracy, precision, recall, and area under the receiver operating curve (AUC-ROC) were used to assess the effectiveness of the model. The SHAP values provide insights into the significance and influence of particular genes that are associated with sarcopenia. The genes that are obtained from the results are utilized for further analysis.

2.5. Protein-protein construction

Identified top genes from the analysis were mapped to construct interaction using the STRING database, which helps to understand the biological interactions of proteins based on sarcopenia. The network obtained from the STRING was further analyzed to predict the miRNA-mRNA.

2.6. miRNA-mRNA interaction

Genes are constructed using the STRING database was obtained to predict the miRNA-mRNA in Encori database (https://rnasysu.com/encori/). Further, the genes and miRNA-mRNA were imported into the Cytoscape software to know the degree of score and to find out the significant roles in gene regulation. This helps in finding out the potential biomarker for sarcopenia based on the interaction with genes and the degree of score.

3. Results

The combined dataset was analyzed using XG-Boost and SHAP the explainable artificial intelligence to get insight into significant potential biomarkers of sarcopenia. The dataset was obtained based on with or without muscle loss patients in the GEO database. The dataset was processed for XG-Boost analysis to have high accuracy and precision hence the model demonstrated a strong predictive performance of accuracy of 97 percent, all of which its ability to differentiate between sarcopenia and low muscle mass. The model was split into x train, y train, x test, and y test with the test size of 0.2 and random state value of 42. SHAP analysis helps in predicting the potential genes of large data by contributing to the prediction of the model. SHAP plots of impact model output were obtained based on the LogFC, P. Value, t, Average expression, adj.P.Value, and Base because the dataset contains the expression based on the specific parameter shown in Fig. 1. The waterfall plot of SHAP helps in determining and displaying the cumulating effect of

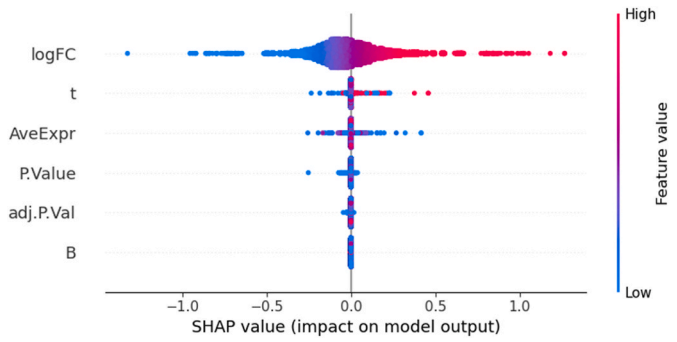

Fig. 1. SHAP Value Plot
SHAP value plot representing the impact of individual gene features on the XGBoost model's output for sarcopenia prediction. Each bar indicates the importance of a gene in the model, with positive SHAP values contributing to sarcopenia prediction and negative values reducing the likelihood. Genes are ranked by their LogFC and adjusted *P*-values.

positive and negative values of the result. The base value represents the model prediction where the contributions of individual features are added or reduced from the base value which helps to show their impact on the prediction. Whereas the cumulative effect of the final value taken as consideration of all contributions shows the model prediction was given in Fig. 2. Top 20 genes predicted by the explainable AI were determined by the scatter plot based on the LogFC and P. Value was represented in Fig. 3. Genes obtained from the prediction model were considered and the protein-protein interaction network was visualized in STRING database. MiRNA-mRNA is regarded as a biomarker based on expression patterns in cells which helps in gaining insight into the genes that are differentially expressed. Expression of mRNA is often associated with the gene level based on the specificity of the cell type and the disease state. This helps in the identification of pathology and biological processes of the differentially expressed genes. After identifying the miRNA-mRNA of the predicted genes we construct an interaction network between the genes and miRNA-mRNA this helps in finding the best score and potential biomarker for sarcopenia. MiR-186–5p has the best score among all the MiRs. The score of miRNA-mRNA is given in Table 1, Whereas the interaction network is shown in Fig. 4.

4. Discussion

Sarcopenia is characterized by progressive muscle loss due to various

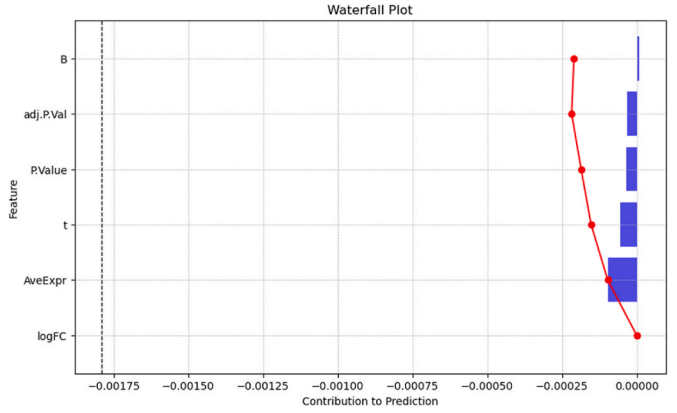

Fig. 2. Waterfall Plot of Feature Contributions
Waterfall plot illustrating the cumulative effect of SHAP values on the final model prediction. The base value represents the expected model output, while each gene's contribution is shown as an increase or decrease from the baseline. Higher contributions suggest stronger relevance to sarcopenia-related gene expression patterns.

factors such as age, gender, and physical activity with various pathological responses including inflammation, endocrine dysfunction, and metabolic changes. So, there is a need to identify a biomarker to address the multifactorial nature of sarcopenia (El-Sebaie and Elwakil, 2023). In this study, we utilized a system biology approach to identify a potential biomarker for sarcopenia. Among older adults, sarcopenia is highly prevalent. As people age normally, they experience a steady and widespread degenerative degeneration of skeletal muscle mass, quality, and strength (Wiedmer et al., 2021). The pathophysiology of sarcopenia is complicated, and finding new, precise molecular markers that are reliable and useful for sarcopenia evaluation, therapy, or prognosis assessment may be challenging. The advancement of omics methods and bioinformatics technology presents fresh chances to find novel targets that will aid in our comprehension of the pathogenesis of sarcopenia. Drawing from the GSE111006, GSE111010, and datasets, we developed STRING in this study to find co-expression genes and potential biochemical pathways associated with sarcopenia. The goal of the current work is to discover the functional genes associated with the disease and the critical miRNAs that are involved in the development of sarcopenia. The analysis of gene ontology, gene enrichment pathways, PPI, hub genes, and miRNA-mRNA interactions is at the center of this entire research project. Twenty genes were identified to be changed in the sarcopenia patient in the current study. Later, six important nodes, including NTRK2, PCK1, DSP, SCD, MMRN1, and EDIL3, were identified in the interaction network amongst miRNA-hub genes. As a result, the current investigation identified a crucial miRNA called hsa-miR-186–5p, which is aimed at over 50% of the hub genes. Therefore, it indicates that this specific miRNA plays a significant role in the pathophysiology of sarcopenia. Protein known as TrkB (tropomyosin receptor kinase B) is encoded by the NTRK2 gene, often referred to as neurotrophic receptor tyrosine kinase 2. The neurotrophins receptor TrkB is used to bind to neurotrophins such NT-4 (neurotrophin-4) and brain-derived neurotrophic factor (BDNF). For the growth, survival, and functionality of neurons in the nervous system, these neurotrophins are essential. Numerous mental and neurological conditions are linked to it. Major Depressive Disorder (MDD) (Torres et al., 2017) is one prominent illness associated with mutations or deregulation of the NTRK2 gene. Studies on NTRK2 connection have been published for neurological illnesses like autism and Alzheimer's illness. (Chen et al., 2008) (Vepsäläinen et al., 2005; Zeng et al., 2013). The process of gluconeogenesis—the synthesis of glucose from non-carbohydrate sources—is the main function of the PCK1 gene, which codes for the enzyme phosphoenolpyruvate carboxykinase 1 (Beale et al., 2007). Several genes have been linked to type 2 diabetes mellitus, including PCK1. Most people assume that hepatic gluconeogenesis produces too much glucose as a result of PCK1 mutations. Alternatively, abnormalities at the PCK1 locus may influence PCK1 expression in fat tissue in a specific way. Changes in glyceroneogenesis would follow, affecting how fatty acids are stored and released (Beale et al., 2004). Furthermore, overexpression of the PCK1 gene is known to inhibit glycolysis pathways and activate gluconeogenesis, which in turn antagonizes hepatocellular carcinoma (Tang et al., 2018). The role of PCK1 in sarcopenia—the age-related decrease of muscle mass and function has not been well investigated or proven. The primary function of the DSP gene, which gene for the protein desmoplakin, is to anchor intermediate filaments to desmosomal plaques in cells, hence preserving the structural integrity of tissues (Favre et al., 2018). A genetic cardiac conduction disease linked to a DSP gene mutation. Functional studies verified that ion channel remodeling and malfunction regulate the primary arrhythmogenic effect of DSG (Cerrone et al., 2012; Noorman et al., 2013; Rizzo et al., 2012; Yu et al., 2014). Although direct research connecting mutations in the DSP gene to sarcopenia is lacking, studies investigating more general relationships between desmosomal proteins and muscle function have been conducted. By accelerating the production of monounsaturated fatty acids, specifically oleic acid (18:1n-9), from saturated fatty acids, the SCD gene which encodes stearoyl-CoA desaturase plays a critical role in lipid metabolism

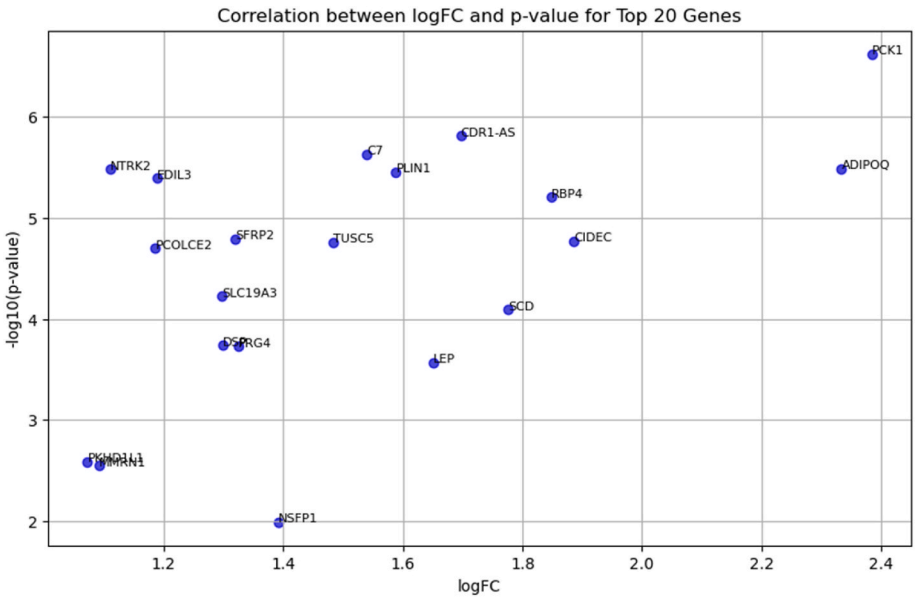

Fig. 3. Top 20 Predicted Genes Based on LogFC and *P*-Value
Scatter plot displaying the top 20 differentially expressed genes (DEGs) identified by XG-Boost and SHAP analysis. The x-axis represents LogFC, while the y-axis represents the -log10(*P*-value), highlighting the genes with the most significant expression changes in sarcopenia patients compared to controls.

Table 1
Predicted Biomarker Scores and Ranks
Top-ranked hub genes and miRNAs based on interaction scores. MiR-186–5p leads as the primary miRNA biomarker with a score of 36, followed by key genes like NTRK2, SCD, and EDIL3.

Rank	Name	Score
1	NTRK2	911
2	SCD	588
3	EDIL3	289
4	MMRN1	113
5	DSP	85
6	hsa-miR-186–5p	35
7	hsa-miR-513a-5p	25
8	PCK1	23
9	hsa-miR-27a-3p	20
10	hsa-miR-522–3p	19

(Calvo et al., 2019). Since changes in the composition of phospholipids have been linked to several diseases, including cancer, diabetes, and cardiovascular ailments, SCD1 is particularly interesting. SCD1 has also been linked to the occurrence of obesity and metabolic syndrome since oleic acid, the primary result of the SCD1 reaction, is the principal fatty acid of human fat tissue triacylglycerols (Mauvoisin and Mounier, 2011).Changes in lipid metabolism may have an indirect effect on muscle health, even though there is no direct evidence connecting the SCD gene to sarcopenia. Multimerin-1, a large glycoprotein found in the extracellular matrix and involved in angiogenesis and blood coagulation, is encoded by the MMRN1 gene. The function of MMRN1 in cancer has come to light in the last several years. However, there aren't many systematic investigations in this field (Zhou et al., 2024). DEL1 (Developmental Endothelial Locus-1) and EDIL3 (EGF-like repeat and discoidin I-like domain-containing protein 3) are two more names for the same protein, which is involved in tissue remodeling and cell adhesion, especially in angiogenesis and vascular development. It can also produce big, branching matrix fibers by self-associating. As a crucial regulator of coagulation, coagulation factor V is bound by multimerin 1 in platelet α-granules (Jeimy et al., 2008). Encoded by the human MIR186 gene, MiR-186–5p, often referred to as hsa-miR-186–5p, is a microRNA molecule. Numerous diseases and biological processes have been linked to miR-186–5p. Based on scientific research, it may contribute to cancer by affecting the growth of cells, the death of cells, and the spread of various tumor forms. Further research has examined its potential impact on neuronal development and function in the context of neurological conditions. It was proposed that miR-186–5p might be a marker for diagnosis and a possible therapeutic target for individuals with ischemic stroke since it caused neuron death and suppressed IGF-1 in the ischemia stroke model (Wang et al., 2018). In AC16 cardiomyocytes, miR-186–5p contributes to HG-induced cytotoxicity and death (Jiang et al., 2018). A study states that miR-186–5p is majorly associated with pathways that are related to muscle metabolism, hypertrophy, and response to exercise (Millet et al., 2024). Through this study we observed that The SCD1 gene and muscle function are indirectly linked through SCD1's role in fat metabolism. Multimerin-1 (MMRN1) is a gene involved in blood clotting and may play a role in muscle health. MiR-186–5p, encoded by MIR186, is a microRNA potentially affecting muscle metabolism and response to exercise.

5. Conclusion

Biomarkers for sarcopenia are still controversial. This study helps to identify potential biomarkers for sarcopenia by using the commonly available patient dataset. AI and ML play a vital role in identifying enormous amounts of data based on our needs. These discoveries point to possible targets for diagnosis and treatment in addition to expanding our knowledge of the molecular landscape of sarcopenia. Future research should confirm these indicators through experimental investigations, investigate their physiological functions in muscle tissue, and evaluate their clinical usefulness across a range of groups, even though this work offers a solid basis. These initiatives may open the door to more accurate diagnostic instruments and individualized treatment plans for the treatment of sarcopenia.

CRediT authorship contribution statement

Sarvesh Sabarathinam: Writing – review & editing, Writing – original draft, Conceptualization. **Akash Jayaraman:** Formal analysis. **Ramesh Venkatachalapathy:** Formal analysis. **Subhiksha Shekar:** Software.

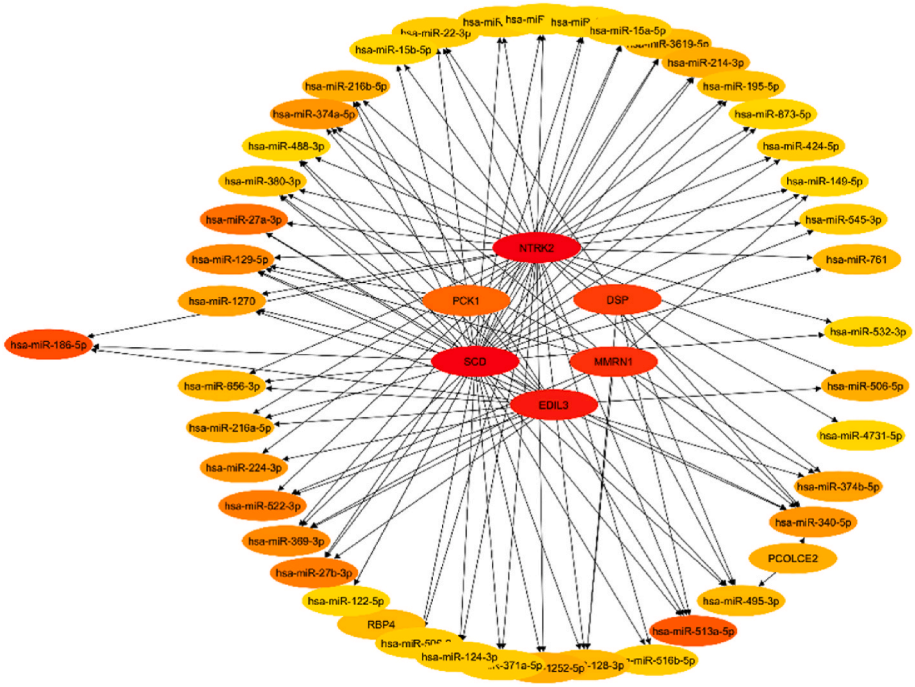

Fig. 4. MiRNA-mRNA Interaction Network
Network visualization generated using Cytoscape, showing interactions between hub genes and predicted miRNAs based on the STRING and Encori databases. Node size corresponds to the degree score, with miR-186–5p having the highest score (36). Edges represent the predicted regulatory interactions between miRNAs and mRNAs.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Ethical approval

Not applicable.

Availability of data and materials

Supporting materials have attached in Supplementary section as separate file.

Funding

No funding has been received for this research work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amolm.2025.100070.

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