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Identification of diagnostic microRNAs and their target genes in multiple sclerosis based on interactome networks using an in silico approach

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MicroRNAs; Multiple Sclerosis; Biomarkers; Gene Expression; Diagnosis

Abstract

Background: The most common demyelinating disease of nerve fibers in the brain and spinal cord is multiple sclerosis (MS) which is associated with several disabilities. By early diagnosis and treatment of MS, the progression of disability can be slowed down. For this purpose, our study aims to identify diagnostic micro ribonucleic acids (miRNAs) and their target genes in MS.

Methods: For the screening of up-regulated and down-regulated genes and miRNAs in patients with MS, GSE17846 (platform: GPL9040, 20 MS samples and 21 control samples), GSE108000 (platform: GPL570, 7 chronic active MS lesions, 8 inactive MS lesions, and 10 controls), and GSE135511 (platform: GPL6883, 20 cases of MS and 10 controls) were extracted from the Gene Expression Omnibus (GEO) database and analyzed based on criteria |log2 (fold change)| > 1 and P-value < 0.05. Protein-protein and miRNA-messenger ribonucleic acid (mRNA) interaction networks were constructed by Cytoscape version 3.9.1 and then, miRNAs and common target genes were detected in MS. Finally, functional enrichment analysis of common target genes was obtained.

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Results: 9 diagnostic miRNAs, including hsa-miR-107, hsa-miR-574-5p, hsa-miR-1206, hsa-miR-142-3p, hsa-miR-1275, hsa-miR-140-5p, hsa-miR-1207-5p, hsa-miR-613, and hsa-miR-1258 were identified. We also detected 12 target genes for these miRNAs involved in MS. The genes were PLXDC2, Potassium voltage-gated channel subfamily C member 1 (KCNC1), FCGBP, MS4A6A, SNAP25, CCL2, FGF13, GABRG2, SLC5A3, KCNC2, MAL2, and HTR5A.

Conclusion: This research introduces miRNAs and their target genes associated with MS as biomarkers to develop new diagnostic and treatment methods. However, this research can be enhanced by additional validation procedures, such as in vitro and in vivo tests of these discovered biomarkers.

Introduction

The nervous system's axons are surrounded by a lipid-rich protective membrane structure called the myelin sheath. This coating acts as insulation and is necessary for the proper functioning of the nervous system in vertebrates. The myelin sheath plays an important role in the rapid impulse transmission along the axon.[1] In young adults, multiple sclerosis (MS) is the most frequent demyelinating cause in the various regions of the central nervous system (CNS) which is mediated by an autoimmune dysfunction.[1,2] In this disease, aberrant autoantibodies mistakenly attack myelin and damage it. Nerve conduction is blocked by demyelination. Lesions in the CNS lead to severe physical or cognitive disability and neurological problems. In particular, demyelination of the spinal cord causes significant neurological disabilities in patients.[2,3] In recent decades, the incidence and prevalence of MS have been increasing in developed and developing countries which is associated with an enormous economic burden.[4]

MS is still a complex and unknown disease. The multiple risk factors for this disease have been mentioned. Smoking, gender, being infected with some viruses, having low levels of vitamin D, being overweight, and genetic factors are the most important risk factors for MS.[5]

To diagnose MS, laboratory tests and imaging are performed. Delayed diagnosis of MS is a common problem in many countries. Identifying the disease in the early stages has not only shown better treatment results but can also greatly reduce the economic burden. Nowadays, the use of molecular methods is very useful for rapid diagnosis of inflammatory diseases and investigations of treatment responses.[2,6,7] Therefore, detecting sensitive and specific diagnosis biomarkers for MS can be useful in this field.

In a cell, a set of different types of molecular interactions can be shown in the form of biological networks called interactomes. The interactome network displays relationships among various groups of macromolecules such as proteins, carbohydrates, lipids, and nucleic acids. Protein-protein interaction networks (PPINs) and gene regulatory networks (GRNs) are two applicable intercoms.[8-10] PPIN provides useful information about molecular functions and their coordination by showing the physical interactions between proteins in a cell, which is the basis for cellular processes. Therefore, PPIN results can be used to identify key proteins for the development of valuable diagnostic biomarkers. GRNs are employed to identify regulatory modules that impact cellular processes and disease phenotypes. Regulatory interactions between genes that are mediated by transcription factors can be checked well in this type of network. As a result, they are an effective tool for finding biomarkers. The combination of PPINs and GRNs allows us to more precisely identify biomarkers.[11-14]

A wide range of biological processes are controlled by non-coding oligonucleotides called micro ribonucleic acids (miRNAs). Regulatory functions are the most important roles of this class of molecules. Various factors change miRNA expression. In the last decade, it has been proven that one of the factors of miRNA change is diseases; thus, these molecules can be used as biomarkers to diagnose various diseases.[15] Alterations in numerous miRNAs have been reported in many diseases related to the nervous system, including MS, Huntington's disease (HD), Alzheimer's disease (AD), Parkinson's disease (PD), stroke, and epilepsy. Recent research has shown that glial cells and immune cells are strongly affected by miRNAs in MS. A change in the expression of miRNA leads to a change in the expression of a group of genes, which itself leads to a wide change in biological processes.[16-18]

In most studies to investigate potential biomarkers for MS disease, miRNAs or altered proteins have been studied separately or one expression profile has been used for analysis. The merging of the functional interactions between miRNAs and their target genes enables the development of strong biomarkers, which was carried out in this study by analyzing three expression profiles.

Considering the importance of early diagnosis of MS, this study was conducted to find diagnostic biomarkers for this disease. First, up-regulated and down-regulated genes and miRNAs in 3 datasets of the Gene Expression Omnibus (GEO) database were analyzed. Next, miRNA target genes were obtained. Finally, two interactome networks, protein-protein and miRNA-messenger ribonucleic acid (mRNA) interaction networks, were applied to predict diagnostic miRNAs and their target genes in MS.

Materials and Methods

Acquisition of suitable microarray data for MS: The GEO database is an international free repository for access to genomic datasets. In this web-based tool, researchers can access different types of information such as gene expression profile, genome binding/occupancy profile, genome methylation profile, genome variation profile, non-coding ribonucleic acid (ncRNA) profile, and many more.[19] Therefore, the GEO site was used as a high-throughput gene expression data repository to retrieve datasets related to the expression profiles of patients with MS. Data should have both patient samples and healthy controls, they should include miRNA or mRNA expression profiles by an array, and the sample size should be sufficient and available. Quality control measures were performed using the GEOquery R package, which included checking and creating normalization plots of differentially expressed genes (DEGs).

Screening of up-regulated and down-regulated genes and miRNAs: In this step, genes with different expression levels should be identified between healthy and diseased groups. For this purpose, GEO2R was used. GEO2R is a very practical and useful tool in the GEO database, which allows the comparison of expression profiles of several groups. GEO2R uses the R programming language and performs analysis of variance (ANOVA) or t-tests.[20] In this tool, at least 2 up to 10 groups can be analyzed for comparison. Based on $|\log2 \text{ (fold change)}| > 1$ and P-value < 0.05, up-regulated and down-regulated genes and miRNAs were selected.

Detecting diagnostic miRNAs and their target genes in MS: Venn diagram screened common DEGs in GSE108000 and GSE135511 datasets at https://bioinformatics.psb.ugent.be/webtools/Venn/. PPINs were constructed with degrees 1 to 8 for common DEGs. DIANA-microT is a free web server that predicts targets for miRNAs using various biological sources. DIANA-microT relies on curated and high-quality databases, including TarBase and miTG score, to validate miRNA-mRNA interactions.[21] The DIANA-microT 2023 server obtained target genes of differentially expressed miRNAs (DEMs) in GSE17846. Finally, miRNAs with common target genes were filtered and the final miRNAs-mRNAs network was constructed by Cytoscape version 3.9.1 software. Cytoscape is one of the open-source software packages for drawing and modeling different types of networks, such as protein-protein interaction, miRNAs-mRNAs interaction, and long ncRNA (lncRNA)-miRNA-mRNA interaction networks. This software allows the analysis of interactions by three main parameters: betweenness, degree, and closeness.[22] In this study, the degree which is the number of connections of each protein within the network was considered.

Functional enrichment analysis of common target genes: The DAVID program is a useful database for annotation, visualization, and integrated discovery. This program categorizes a list of genes in terms of function by a new algorithm. To analyze common biological pathways related to the overlapped genes, we used the DAVID program at https://david.ncifcrf.gov/. Common DEGs were listed in the search box of the DAVID program; official gene symbol was selected as an identifier. The species was limited to Homo sapiens. In this study, we analyzed two major categories of gene annotation: Gene Ontology (GO) terms, including Biological Process (BP), Molecular Function (MF), Cellular Component (CC), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. We initially considered all GO and KEGG terms provided by DAVID. Finally, five top clusters of functional enrichment analysis in common target genes were filtered with a significance threshold of $P < 0.05$.

Results

Acquisition of suitable microarray data for MS: According to the selection criteria, three gene expression profiles, including GSE17846 with miRNA expression profile, GSE108000, and GSE135511 with mRNA expression profiles, were extracted from the GEO database. All three profiles belonged to humans and had both patient and healthy control samples, sufficient sample size, and the ability to be analyzed with GEO2R. GSE17846 with platform GPL9040 involves 20 MS samples and 21 control samples.

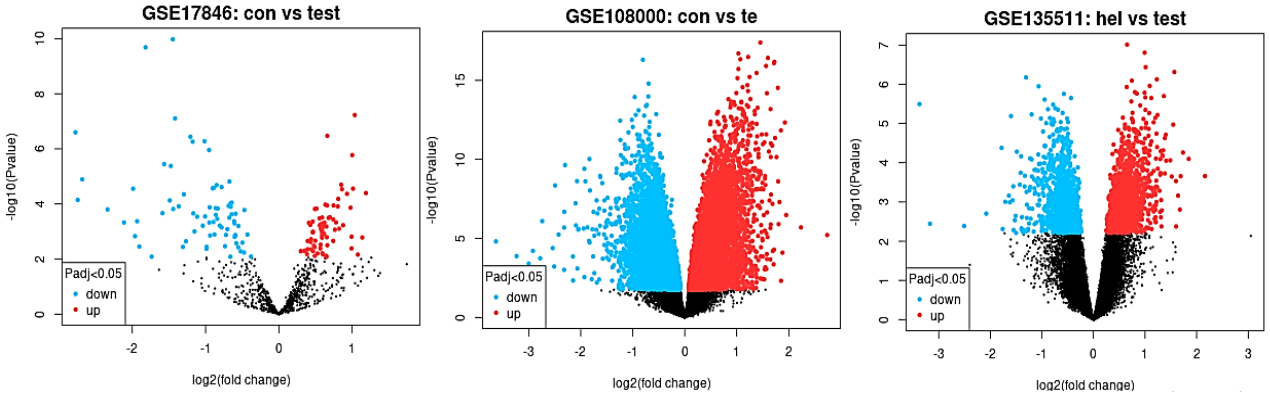

Figure 1. Volcano plots of genes with different expression levels in GSE17846, GSE108000, and GSE135511, respectively

GSE108000 is established on the annotation platform of GPL570 and consists of 7 chronic active MS lesions, 8 inactive MS lesions, and 10 controls. The platform of GSE135511 is GPL6883, and there are 20 cases of MS brains and 10 controls.

Screening of up-regulated and down-regulated genes and miRNAs: Genes with different expression levels were analyzed by GEO2R based on |log2 (fold change)| > 1 and P-value < 0.05. In the dataset GSE17846, 30 up-regulated and 6 down-regulated miRNAs were shown. In GSE108000, DEGs between the healthy and diseased groups with MS lesions were 330 up-regulated and 412 down-regulated genes. About GSE135511, 117 up-regulated and 118 down-regulated genes were detected. Volcano plots of DEGs in 3 datasets are shown in figure 1.

Detecting diagnostic miRNAs and their target genes in MS: After GB_ACC IDs were converted to gene symbols, 636 DEGs in GSE108000 were compared with 227 DEGs in GSE135511 as unique elements by the Venn diagram. Based on the Venn diagram, 33 common DEGs in GSE108000 and GSE135511 were obtained (Figure 2) that 22 genes of which were in interaction in Cytoscape software (Figure 3).

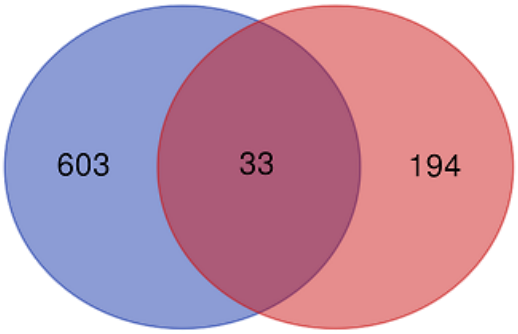

Figure 2. Venn diagram of common differentially expressed genes (DEGs) in GSE108000 (blue circle) and GSE135511 (red circle)

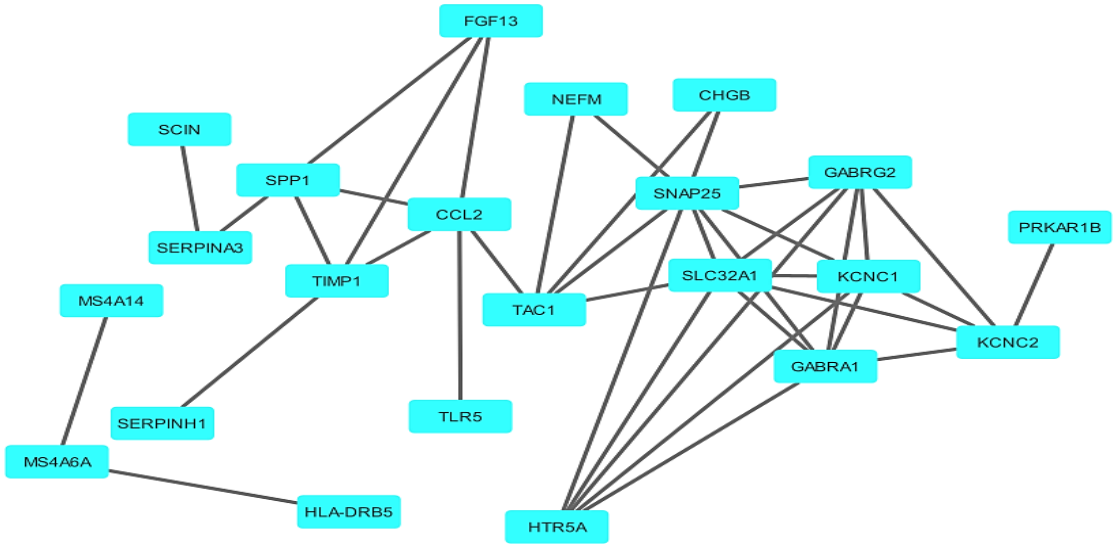

Figure 3. Protein-protein interaction networks (PPINs) of common differentially expressed genes (DEGs) in GSE108000 and GSE135511

Target genes of DEMs in GSE17846 by Cytoscape software, 5996 nods 8233 edges were shown. After filtration of miRNAs with common target genes in GSE108000 and GSE135511, the final miRNAs-mRNAs network was constructed (Figure 4). This network consists of 12 mRNAs including PLXDC2, potassium voltage-gated channel subfamily C member 1 (KCNC1), FCGBP, MS4A6A, SNAP25, CCL2, FGF13, GABRG2, SLC5A3, KCNC2, MAL2, and HTR5A. In our research, hsa-miR-107, hsa-miR-574-5p, hsa-miR-1206, hsa-miR-142-3p, hsa-miR-1275, hsa-miR-140-5p, hsa-miR-1207-5p, hsa-miR-613, and hsa-miR-1258 were identified as 9 key miRNA nods.

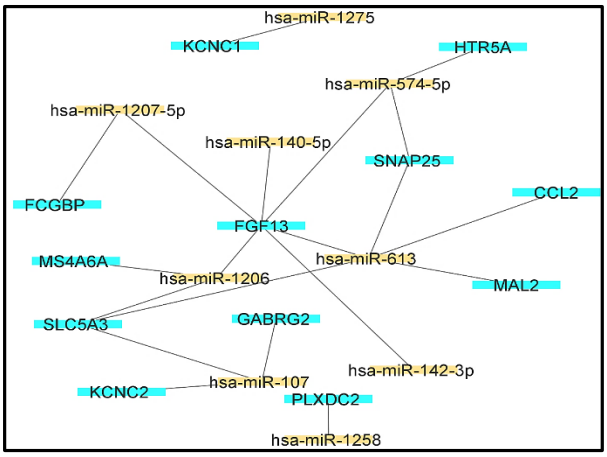

Figure 4. The final micro ribonucleic acids (miRNAs)-messenger ribonucleic acids (mRNAs) network (yellow and blue represent miRNAs and mRNAs, respectively)

Functional enrichment analysis of common target genes: Functional enrichment analysis of common target genes was carried out by the DAVID program. Based on the results of this database, functional clusters were detected. In table 1, the five top clusters with category, term, gene count, P-value, and genes are shown. 33 common DEGs evolve in ion channel binding, synapse, voltage-gated potassium channel activity, presynaptic membrane, and potassium ion transmembrane transport pathways.

Discussion

Cerebrospinal fluid (CSF) analysis, clinical reviews, and magnetic resonance imaging (MRI) results are used in the diagnosis of MS. These methods have several disadvantages, including the possibility of misdiagnosis, high costs, and inconvenience.[23] In recent years, the importance of molecular biomarkers in various fields has been increasingly recognised.[24,25] Due to the relationship between MS and the neuro-immune system, this disease is associated with changes in the expression of many genes in the immune system and the nervous system.[26,27] Several studies have explored the role of miRNAs as diagnostic and prognostic biomarkers.[28,29] In addition to disease diagnosis, miRNAs are also used in the monitoring of diseases and in the evaluation of response to treatment. Considering the importance of identifying biological biomarkers as a non-invasive, cost-effective, and reliable diagnostic tool in the diagnosis of MS, this study was conducted to introduce diagnostic biomarkers in MS. In this study, up- and down-regulated genes and miRNAs were analyzed in three datasets (GSE17846, GSE108000, and GSE135511), target genes of miRNAs were extracted, functional enrichment analyses on common target genes were performed, and a network of miRNAs was finally constructed.

According to our findings, in the miRNAs-mRNAs network, 12 mRNAs which include PLXDC2, KCNC1, FCGBP, MS4A6A, SNAP25, CCL2, FGF13, GABRG2, SLC5A3, KCNC2, MAL2, and HTR5A are among the hub DEGs in MS disease. Additionally, hsa-miR-107, hsa-miR-574-5p, hsa-miR-1206, hsa-miR-142-3p, hsa-miR-1275, hsa-miR-140-5p, hsa-miR-1207-5p, hsa-miR-613, and hsa-miR-1258 were identified as 9 top miRNA nods.

Table 1. Top clusters of functional enrichment analysis of 33 common target genes

Category	Term	Gene count	Statistical P	Genes
GOTERM_MF_DIRECT	Ion channel binding	5	8.53E-05	SNAP25, KCNC1, KCNC2, FGF13, SLC5A3
UP_KW_CELLULAR_COMPONENT	Synapse	6	0.002091	SNAP25, GABRA1, KCNC1, SLC32A1, KCNC2, GABRG2
GOTERM_MF_DIRECT	Voltage-gated potassium channel activity	3	0.004889	SNAP25, KCNC1, KCNC2
GOTERM_CC_DIRECT	Presynaptic membrane	3	0.016453	SNAP25, KCNC1, KCNC2
GOTERM_BP_DIRECT	Potassium ion transmembrane transport	3	0.017882	SNAP25, KCNC1, KCNC2

Our results show that synaptosomal-associated protein 25 (SNAP25) is one of the major DEGs in MS. In the miRNAs-mRNAs network, hsa-miR-574-5p and hsa-miR-613 affect the expression of the SNAP25 gene. This gene interferes with ion channel binding, voltage-gated potassium channel activity, synapse, presynaptic membrane, and potassium ion transmembrane transport. Synaptic dysfunction in MS is one of the reasons for the delay in message transmission in patients with MS.[30] Due to the important actions of SNAP25 in the synapse, changes in the regulation of the expression of this gene may be related to this disorder. SNAP25 is important in synaptic transmission and neurotransmitter release. Based on the studies, miR-146a affects the expression of SNAP25, and thus can play a role in demyelination and axonal loss.[31] In addition, Xu et al. reported that hsa-miR-574-5p and hsa-miR-613 were among the key DEMs in MS formation.[32]

The plexin domain containing 2 (PLXDC2) is a membrane protein expressed in the developing nervous system. According to Wirz et al., this gene has been significantly upregulated in AD in both mouse and human datasets.[33] PLXDC2 was regulated by hsa-miR-1258 in the miRNAs-mRNAs network.

Based on our findings, KCNC1 and KCNC2 of the KCNC family have a significant expression change in patients with MS. KCNC family are voltage-gated K (+) channels that play pivotal roles in mammalian brains. Hsa-miR-1275 and hsa-miR-107 play a role in changing the expression of KCNC1 and KCNC2 genes, respectively. In many studies, the role of both miRNAs in various neurological diseases has been shown. Zhao et al. found significant dysregulation of hsa-miR-1275 in neurological disorders and introduced it as a novel biomarker in epilepsy.[34] Additionally, overexpression of hsa-miR-1275 was reported in patients with PD.[35] Leidinger et al. studied miRNAs in the blood samples of 48 patients with AD and 22 healthy controls, and based on their results, hsa-miR-107 could be used as a biomarker for the monitoring of AD.[36]

Liu et al., in their work on two datasets (GSE17048 and GSE41848), reported that MS4A6A, together with six other genes, was one of the key genes in the screening of MS.[37] The change in the expression level of this gene has been demonstrated in other neurological diseases, including AD. In the study conducted by Proitsi et al., high levels of MS4A6A have been mentioned in AD.[38] In our miRNAs-mRNAs network, the MS4A6A gene is regulated by hsa-miR-1206.

One possible treatment strategy for MS has been proposed: targeting the fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) system.[39] Fibroblast growth factor 13 (FGF13) is expressed in cerebral cortical neurons, and this protein is involved in the regeneration of peripheral nerves.[40] In Zhang et al.'s research, which focused on the role of the fibroblast growth factor (FGF) signaling pathway in MS disease, FGF/FGFR signaling was mentioned as a promising strategy for the treatment of patients with MS.[39] In our miRNAs-mRNAs network, hsa-miR-107, hsa-miR-1206, hsa-miR-142-3p, hsa-miR-140-5p, and hsa-miR-613 are directly effective in regulating the expression of this gene.

Conclusion

Due to the increasing incidence rate and gradual progression of neurological diseases such as MS, early diagnosis and treatment have become the main priority. In recent years, miRNAs have emerged as important biological biomarkers with significant implications for medical science.

This in silico study identified 9 diagnostic miRNAs and 12 of their target genes in MS. Although many diagnostic biomarkers have been recognized in different diseases in recent years, most of them require in vitro and in vivo validation processes. In our research, the related genes of miRNA are analyzed by the database and software, which is a limitation of this study. Larger clinical trials to confirm the diagnostic and prognostic value of identified biomarkers, study the expression profile of detected biomarkers in different stages of patients with MS, and accurately investigate their functional mechanisms in MS disease can confirm and complement this research.

Conflict of Interests

The authors declare no conflict of interest in this study.

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References

1. Stadelmann C, Timmler S, Barrantes-Freer A, Simons M. Myelin in the Central Nervous System: Structure, Function, and Pathology. Physiol Rev 2019; 99(3): 1381-431.
2. Dobson R, Giovannoni G. Multiple sclerosis - a review. Eur J Neurol 2019; 26(1): 27-40.
3. Ghasemi N, Razavi S, Nikzad E. Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy. Cell J 2017; 19(1): 1-10.
4. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler 2020; 26(14): 1816-21.
5. Yuan S, Xiong Y, Larsson SC. An atlas on risk factors for multiple sclerosis: A Mendelian randomization study. J Neurol 2021; 268(1): 114-24.
6. Arneth B, Kraus J. Laboratory biomarkers of Multiple Sclerosis (MS). Clin Biochem 2022; 99: 1-8.
7. Yang J, Hamade M, Wu Q, Wang Q, Axtell R, Giri S, et al. Current and Future Biomarkers in Multiple Sclerosis. Int J Mol Sci 2022; 23(11): 5877.
8. Ghadie MA, Coulombe-Huntington J, Xia Y. Interactome evolution: insights from genome-wide analyses of protein-protein interactions. Curr Opin Struct Biol 2018; 50: 42-8.
9. Rabbani G, Baig MH, Ahmad K, Choi I. Protein-protein Interactions and their Role in Various Diseases and their Prediction Techniques. Curr Protein Pept Sci 2018; 19(10): 948-57.
10. Caldera M, Buphamalai P, Müller F, Menche J. Interactome-based approaches to human disease. Curr Opin Syst Biol 2017; 3: 88-94.
11. Liu W, Rajapakse JC. Fusing gene expressions and transitive protein-protein interactions for inference of gene regulatory networks. BMC Syst Biol 2019; 13(Suppl 2): 37.
12. Xin J, Ren X, Chen L, Wang Y. Identifying network biomarkers based on protein-protein interactions and expression data. BMC Med Genomics 2015; 8 Suppl 2(Suppl 2): S11.
13. Vlaic S, Conrad T, Tokarski-Schnelle C, Gustafsson M, Dahmen U, Guthke R, et al. ModuleDiscoverer: Identification of regulatory modules in protein-protein interaction networks. Sci Rep 2018; 8(1): 433.
14. Mercatelli D, Scalambra L, Triboli L, Ray F, Giorgi FM. Gene regulatory network inference resources: A practical overview. Biochim Biophys Acta Gene Regul Mech 2020; 1863(6): 194430.
15. Huang W. MicroRNAs: Biomarkers, Diagnostics, and Therapeutics. In: Huang J, Borchert GM, Dou D, Huan J, Lan W, Tan M, et al., editors. Bioinformatics in MicroRNA Research. New York, NY: Springer; 2017. p. 57-67.
16. Wang J, Chen J, Sen S. MicroRNA as Biomarkers and Diagnostics. J Cell Physiol 2016; 231(1): 25-30.
17. Cao DD, Li L, Chan WY. MicroRNAs: Key Regulators in the Central Nervous System and Their Implication in Neurological Diseases. Int J Mol Sci 2016; 17(6): 842.
18. Doroszkiewicz J, Groblewska M, Mroczko B. Molecular Biomarkers and Their Implications for the Early Diagnosis of Selected Neurodegenerative Diseases. Int J Mol Sci 2022; 23(9): 4610.
19. Clough E, Barrett T. The Gene Expression Omnibus Database. Methods Mol Biol 2016; 1418: 93-110.
20. Li L, Liu X, Ma X, Deng X, Ji T, Hu P, et al. Identification of key candidate genes and pathways in glioblastoma by integrated bioinformatical analysis. Exp Ther Med 2019; 18(5): 3439-49.
21. Maragkakis M, Reczko M, Simossis VA, Alexiou P, Papadopoulos GL, Dalamagas T, et al. DIANA-microT web server: elucidating microRNA functions through target prediction. Nucleic Acids Res 2009; 37(Web Server issue): W273-6.
22. Doncheva NT, Morris JH, Gorodkin J, Jensen LJ. Cytoscape StringApp: Network Analysis and Visualization of Proteomics Data. J Proteome Res 2019; 18(2): 623-32.
23. Ebrahimkhani S, Vafaee F, Young PE, Hur SSJ, Hawke S, Devenney E, et al. Exosomal microRNA signatures in multiple sclerosis reflect disease status. Sci Rep 2017; 7(1): 14293.
24. Burke HB. Predicting Clinical Outcomes Using Molecular Biomarkers. Biomark Cancer 2016; 8: BIC.S33380.
25. Asadzadeh A, Ghorbani N, Dastan K. Identification of druggable hub genes and key pathways associated with cervical cancer by protein-protein interaction analysis: An in silico study. Int J Reprod Biomed 2023; 21(10): 809-18.
26. Patsopoulos NA, De Jager PL. Genetic and gene expression signatures in multiple sclerosis. Mult Scler 2020; 26(5): 576-81.
27. Cordiglieri C, Baggi F, Bernasconi P, Kapetis D, Faggiani E, Consonni A, et al. Identification of a gene expression signature in peripheral blood of multiple sclerosis patients treated with disease-modifying therapies. Clin Immunol 2016; 173: 133-46.
28. Saeidi NN, Dabiri A, Mansouri R, Moomivand A, Goudarzvand M. miRNAs as Valuable Diagnostic Biomarkers in Patients with Multiple Sclerosis. J Biomed Res Environ Sci 2023; 4(4): 773-8.
29. Regev K, Paul A, Healy B, von Glenn F, Diaz-Cruz C, Gholipour T, et al. Comprehensive evaluation of serum microRNAs as biomarkers in multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 2016; 3(5): e267.
30. Bellingacci L, Mancini A, Gaetani L, Tozzi A, Parnetti L, Di Filippo M. Synaptic Dysfunction in Multiple Sclerosis: A Red Thread from Inflammation to Network Disconnection. Int J Mol Sci 2021; 22(18): 9753.
31. Martin NA, Molnar V, Szilagyi GT, Elkjaer ML, Nawrocki A, Okarmus J, et al. Experimental Demyelination and Axonal Loss Are Reduced in MicroRNA-146a Deficient Mice. Front Immunol 2018; 9: 490.
32. Xu ZB, Feng X, Zhu WN, Qiu ML. Identification of key genes and microRNAs for multiple sclerosis using bioinformatics analysis. Medicine (Baltimore) 2021; 100(48): e27667.
33. Wirz KT, Bossers K, Stargardt A, Kamphuis W, Swaab DF, Hol EM, et al. Cortical beta amyloid protein triggers an immune response, but no synaptic changes in the APPswe/PS1dE9 Alzheimer's disease mouse model. Neurobiol Aging 2013; 34(5): 1328-42.
34. Zhao Y, Lu C, Wang H, Lin Q, Cai L, Meng F, et al. Identification of hsa-miR-1275 as a Novel Biomarker Targeting MECP2 for Human Epilepsy of Unknown Etiology. Mol Ther Methods Clin Dev 2020; 19: 398-410.
35. Salemi M, Marchese G, Lanza G, Cosentino FII, Salluzzo MG, Schillaci FA, et al. Role and Dysregulation of miRNA in Patients with Parkinson's Disease. Int J Mol Sci 2022; 24(1): 712.
36. Leidinger P, Backes C, Deutscher S, Schmitt K, Mueller SC, Frese K, et al. A blood based 12-miRNA signature of Alzheimer disease patients. Genome Biol 2013; 14(7): R78.
37. Liu Y, Zhou Y, Yue H, Dou H, Rang X, Wang X, et al. Identification of potential key genes and immune infiltration in Multiple sclerosis. Mult Scler Relat Disord 2022; 60: 103748.
38. Proitsi P, Lee SH, Lunnon K, Keohane A, Powell J, Troakes C, et al. Alzheimer's disease susceptibility variants in the MS4A6A gene are associated with altered levels of MS4A6A expression in blood. Neurobiol Aging 2014; 35(2): 279-90.
39. Zhang Q, Chen Z, Zhang K, Zhu J, Jin T. FGF/FGFR system in the central nervous system demyelinating disease: Recent progress and implications for multiple sclerosis. CNS Neurosci Ther 2023; 29(6): 1497-511.
40. Li R, Tao X, Huang M, Peng Y, Liang J, Wu Y, et al. Fibroblast Growth Factor 13 Facilitates Peripheral Nerve Regeneration through Maintaining Microtubule Stability. Oxid Med Cell Longev 2021; 2021: 5481228.