

Deregulation of Serum MicroRNA Associated with Late-onset Alzheimer’s Disease in Large-scale Japanese Cohort

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Sharlee Climer, University of Missouri – St. Louis, USA

A network modeling analysis of serum microRNA (miRNA) levels for late-onset Alzheimer’s disease (AD) individuals reveals two significant associations between pairs of miRNA and the phenotype. These associations are also significant in held-out validation data. These patterns provide clues that might fuel hypotheses regarding the mechanisms of miRNAs in AD individuals and also provide potential serum biomarkers.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
- Exosomes are membrane-bound extracellular vesicles formed in the endosomal compartments of most eukaryotic cells. - Released by cells, exosomes transport proteins, lipids, and nucleic acids, serving as vital informational molecules for cell-to-cell transfer. - Their abundant presence makes serum exosomes promising candidates for biomarkers and therapeutic targets. - Specifically, microRNAs (miRNAs) represent essential components of exosomes, playing a significant role in regulating cellular processes such as proliferation, differentiation, and apoptosis. - In this study, we modeled miRNA expression levels in late-onset Alzheimer's disease (AD) patients and normal controls as a network, aiming to identify AD-associated biomarker patterns.	- Serum miRNA levels from 1,601 Japanese individuals were obtained from NCBI's Gene Expression Omnibus (Series GSE120584). - After cleaning and normalizing: miRNA levels for 2,562 markers from 1,021 AD cases and 288 normal controls. - The individuals were split into Discovery and Validation datasets. Gender and age were balanced as much as possible between the two datasets. - The Discovery dataset was used to construct a network model with Maestro, our custom tool designed to identify subtypes within heterogeneous data. - The significantly-associated modules were tested for associations in the independent Validation dataset using both the 95% confidence interval of the odds ratio and Youden's J statistic with 10,000 randomizations of phenotype labeling with Bonferroni corrections for multiple testing applied.	- The developed network displayed a robust community structure. - The network was comprised of 11 interconnected modules with sizes varying from 2 to 106 vertices. Over 97% of the vertices were isolated, lacking adjacent edges. - Three modules showed significant associations in the Discovery data and two of these were also significant in the independent Validation data. Module 9: - Low expression of both hsa-mir6885-5p and hsa-mir128-2-5p. - Validation: 266(39.1%) Cases, 26(26.5%) Controls - Odds ratio: 1.779 [1.107,2.859], Youden J: 0.126, YJ pval: 0.000 Module 11: - High expression of both hsa-mir125b and hsa-mir125a. - Validation: 354(52.1%) Cases, 36(36.7%) Controls - Odds ratio: 1.870 [1.208,2.896], Youden J: 0.153, YJ pval: 0.000	- Chronic inflammation in the brain is frequently seen in AD and plays a role in generating oxidative stress. - mir-125b has been associated with neuroinflammation and has been associated with AD¹. - Also, mir-125b is notably upregulated by NF-kB, a pro-inflammatory transcription factor². - Interestingly, mir-125b is a negative regulator of p53, a primary stress response regulator³. - Currently, the biological mechanisms of the other three identified miRNAs remain unclear. - However, their strong associations with both the Discovery and independent Validation groups suggest they could serve as biomarkers, readily detectable through blood tests.	1. Swarbrick S, Wragg N, Ghosh S, Stolzing A. Systematic Review of miRNA as Biomarkers in Alzheimer's Disease. Mol Neurobiol. 2019 Sep;56(9):6156-6167. doi: 10.1007/s12035-019-1500-y. Epub 2019 Feb 8. PMID: 30734227; PMCID: PMC6682547. 2. Lukiw WJ, Alexandrov PN. Regulation of complement factor H (CFH) by multiple miRNAs in Alzheimer's disease (AD) brain. Mol Neurobiol. 2012 Aug;46(1):11-9. doi: 10.1007/s12035-012-8234-4. PMID: 22302353; PMCID: PMC3703615. 3. Le MT, Teh C, Shyh-Chang N, Xie H, Zhou B, Korzh V, Lodish HF, Lim B. MicroRNA-125b is a novel negative regulator of p53. Genes Dev. 2009 Apr 1;23(7):862-76. doi: 10.1101/gad.1767609. Epub 2009 Mar 17. PMID: 19293287; PMCID: PMC2666337. CONTACT  Sharlee Climer Associate Professor Dept. of Computer Science University of Missouri – St. Louis St. Louis, MO, USA climer@umsl.edu 