



Circulating Brain-enriched And Inflammatory MicroRNAs As Blood Biomarkers Of Mild Cognitive Impairment To Alzheimer's Progression

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BACKGROUND

Minimally invasive diagnostic tools are critical to characterize heterogeneous patient mild cognitive impairment (MCI), pre-MCI, and Alzheimer’s disease (AD) dementia populations. microRNAs are short, non-coding regulatory molecules whose expression is dynamically altered in disease, making them promising blood-based biomarkers of neurological dysfunction. We selected microRNAs enriched in specific brain regions, present in synapses, and detectable in blood plasma and analyzed their expression in plasma samples from MCI and AD patients, including a cohort whose diagnosis progressed from MCI to AD.

MATERIALS & METHODS

Expression of 24 brain-enriched and inflammation-associated microRNAs (CogniMIR[®]) was measured and analyzed in 84 amyloid-positive study participants (42 MCI and 42 dementia due to AD), a subset of 295 plasma samples (120 CU, 121 MCI, 54 AD dementia) collected at the University of Pennsylvania ADRC with subgroup comparison data reported previously. Plasma samples of a separate 25 MCI to dementia progressors group, collected at MCI baseline and clinical diagnosis change, were processed under identical protocol.

The CogniMIR[®] panel consists of the microRNAs let-7e-5p, miR-107, miR-125b-5p, miR-127-3p, miR-128-3p, miR-132-3p, miR-134-5p, miR-146a-5p, miR-155-5p, miR-16-5p, miR-181a-5p, miR-323a-3p, miR-335-5p, miR-370-3p, miR-382-5p, miR-409-3p, miR-433-3p, miR-451a, miR-487b-3p, miR-491-5p, miR-7-5p, miR-874-3p, miR-9-5p, and miR-99b-5p.

Cross-sectional Ct data from the 84-participant group was explored for biomarkers separating MCI from AD samples using logistic regression classifiers. Candidate biomarkers were defined as expression ratios between two distinct microRNAs, and biomarkers achieving an area under the receiver operating characteristic curve (AUC) of 0.65 or higher were considered pairs of interest. These qualifying pairs were evaluated for distributional differences between baseline MCI and progression AD samples in the 25 progressors group using a Wilcoxon signed-rank test with Bonferroni correction.

microRNA pair	Accuracy	Sensitivity	Specificity	F1 Score	ROC AUC
miR-487b-3p / miR-134-5p	0.62651	0.59524	0.65854	0.61728	0.69425
miR-491-5p / miR-155-5p	0.63855	0.39024	0.88095	0.51613	0.68728
let-7e-5p / miR-128-3p	0.59524	0.71429	0.47619	0.63830	0.66355
miR-370-3p / miR-134-5p	0.59722	0.94737	0.20588	0.71287	0.66254
miR-491-5p / let-7e-5p	0.61905	0.47619	0.76190	0.55556	0.66128
miR-128-3p / miR-155-5p	0.50602	0.14634	0.85714	0.22642	0.66057
miR-146a-5p / miR-155-5p	0.56627	0.36585	0.76190	0.45455	0.65447
miR-107 / miR-491-5p	0.57143	0.69048	0.45238	0.61702	0.65420

Table 1: Separation of 42 amyloid positive MCI samples from 42 AD samples via logistic regression. Evaluation metrics are shown for 8 microRNA pairs achieving an area under the receiver operating characteristic (ROC) curve above 0.65.

RESULTS

Eight microRNA pairs were deemed sufficiently powerful in classifying amyloid-positive MCI versus AD dementia samples in the 84-sample cohort (Table 1). These biomarkers achieved an AUC ≥ 0.65 and were considered good candidates for testing distributional differences in the separate set of 25 patients progressing from MCI to AD.

Of the eight candidate biomarkers, four showed significant differences between baseline MCI and progression AD samples from the same 25 patients. These microRNA pairs achieved p-values below a Bonferroni-corrected threshold of $p \leq 0.00625$ on a Wilcoxon-signed rank test (Table 2).

microRNA pair	p-value
miR-487b-3p / miR-134-5p	0.00231253
miR-491-5p / miR-155-5p	0.00001633
let-7e-5p / miR-128-3p	0.00000012
miR-370-3p / miR-134-5p	0.24789906
miR-491-5p / let-7e-5p	0.00000012
miR-128-3p / miR-155-5p	0.37475038
miR-146a-5p / miR-155-5p	0.66344357
miR-107 / miR-491-5p	0.00001049

Table 2: p-values from a Wilcoxon signed-rank test comparing baseline MCI samples and progression AD samples in 25 patients. microRNA pairs with a value below the Bonferroni-corrected threshold of $p \leq 0.00625$ are highlighted.

CONCLUSIONS

microRNA pairs formed from the CogniMIR[®] panel demonstrate meaningful ability to separate patients from MCI and AD cohorts.

Certain performant microRNA pairs exhibit statistically significant differences in values from the same patients before and after progressing from MCI to AD.

This establishes a foundation for validation in larger independent cohorts and allows the development of blood-based microRNA panels for early detection and monitoring of Alzheimer's disease progression.

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