Combinatory microRNA serum signatures as classifiers of Parkinson's disease.

https://arctichealth.org/en/permalink/ahliterature299556

Author: Ketan S Patil
Indranil Basak
Ingvild Dalen
Esthelle Hoedt
Johannes Lange
Kristin A Lunde
Ying Liu
Ole-Bjørn Tysnes
Lars Forsgren
Dag Aarsland
Thomas A Neubert
Jan Petter Larsen
Guido Alves
Simon Geir Møller

Author Affiliation: Department of Biological Sciences, St. John's University, New York, NY, USA?

Source: Parkinsonism Relat Disord. 2019 Apr 11; :

Date: Apr-11-2019

Language: English

Publication Type: Journal Article

Abstract:
As current clinical diagnostic protocols for Parkinson's disease (PD) may be prone to inaccuracies there is a need to identify and validate molecular biomarkers, such as circulating microRNAs, which will complement current practices and increase diagnostic accuracy. This study identifies, verifies and validates combinatory serum microRNA signatures as diagnostic classifiers of PD across different patient cohorts.

370 PD (drug naïve) and control serum samples from the Norwegian ParkWest study were used for identification and verification of differential microRNA levels in PD which were validated in a blind study using 64 NY Parkinsonism in UMeå (NYPUM) study serum samples and tested for specificity in 48 Dementia Study of Western Norway (DemWest) study Alzheimer's disease (AD) serum samples using miRNA-microarrays, and quantitative (q) RT-PCR. Proteomic approaches identified potential molecular targets for these microRNAs.

Using Affymetrix GeneChip® miRNA 4.0 arrays and qRT-PCR we comprehensively analyzed serum microRNA levels and found that the microRNA (PARKmiR)-combinations, hsa-miR-335-5p/hsa-miR-3613-3p (95% CI, 0.87-0.94), hsa-miR-335-5p/hsa-miR-6865-3p (95% CI, 0.87-0.93), and miR-335-5p/miR-3613-3p/miR-6865-3p (95% CI, 0.87-0.94) show a high degree of discriminatory accuracy (AUC 0.9-1.0). The PARKmiR signatures were validated in an independent PD cohort (AUC?=?0.71) and analysis in AD serum samples showed PARKmiR signature specificity to PD. Proteomic analyses showed that the PARKmiRs regulate key PD-associated proteins, including alpha-synuclein and Leucine Rich Repeat Kinase 2.

Our study has identified and validated unique miRNA serum signatures that represent PD classifiers, which may complement and increase the accuracy of current diagnostic protocols.

PubMed ID: 31003905 View in PubMed

Familial Danish dementia: co-existence of Danish and Alzheimer amyloid subunits (ADan AND A{beta}) in the absence of compact plaques.

https://arctichealth.org/en/permalink/ahliterature173399
Familial Danish dementia is an early onset autosomal dominant neurodegenerative disorder linked to a genetic defect in the BRI2 gene and clinically characterized by dementia and ataxia. Cerebral amyloid and preamyloid deposits of two unrelated molecules (Danish amyloid (ADan) and beta-amyloid (Abeta)), the absence of compact plaques, and neurofibrillary degeneration indistinguishable from that observed in Alzheimer disease (AD) are the main neuropathological features of the disease. Biochemical analysis of extracted amyloid and preamyloid species indicates that as the solubility of the deposits decreases, the heterogeneity and complexity of the extracted peptides exponentially increase. Nonfibrillar deposits were mainly composed of intact ADan-(1-34) and its N-terminally modified (pyroglutamate) counterpart together with Abeta-(1-42) and Abeta-(4-42) in approximately 1:1 mixture. The post-translational modification, glutamate to pyroglutamate, was not present in soluble circulating ADan. In the amyloid fractions, ADan was heavily oligomerized and highly heterogeneous at the N and C terminus, and, when intact, its N terminus was post-translationally modified (pyroglutamate), whereas Abeta was mainly Abeta-(4-42). In all cases, the presence of Abeta-(X-40) was negligible, a surprising finding in view of the prevalence of Abeta40 in vascular deposits observed in sporadic and familial AD, Down syndrome, and normal aging. Whether the presence of the two amyloid subunits is imperative for the disease phenotype or just reflects a conformational mimicry remains to be elucidated; nonetheless, a specific interaction between ADan oligomers and Abeta molecules was demonstrated in vitro by ligand blot analysis using synthetic peptides. The absence of compact plaques in the presence of extensive neuro fibrillar degeneration strongly suggests that compact plaques, fundamental lesions for the diagnosis of AD, are not essential for the mechanism of dementia.