Genomic biomarkers for Alzheimer disease

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Background

Alzheimer's disease (AD) is the most frequent cause of dementia. Misfolded protein pathological hallmarks of AD are brain deposits of amyloid β (Aβ) plaques and phosphorylated tau neurofibrillary tangles. It has been suggested that some individuals are more prone to Aβ neurotoxicity and hence more likely to develop AD when aging brains start accumulating Aβ plaques. To identify novel AD biomarkers, we initially applied genome-wide transcriptomics of human lymphoblastoid cell lines (LCLs) correlating gene expression levels with in-vitro Aβ sensitivity. Understanding the biology of healthy human aging and dementia-free longevity is key for deciphering the biology of neurodegenerative diseases. We also focused on selected potential biomarkers such as activity-dependent neuroprotective protein (ADNP) (discovered in Prof. Gozes laboratory), which was shown to decrease in AD patient serum samples. Furthermore, ADNP directly regulates the expression of apolipoprotein E (APOE), in a sex-dependent manner, with APOE4 being the major risk gene for sporadic AD.

Aim

Discover new early biomarkers for AD

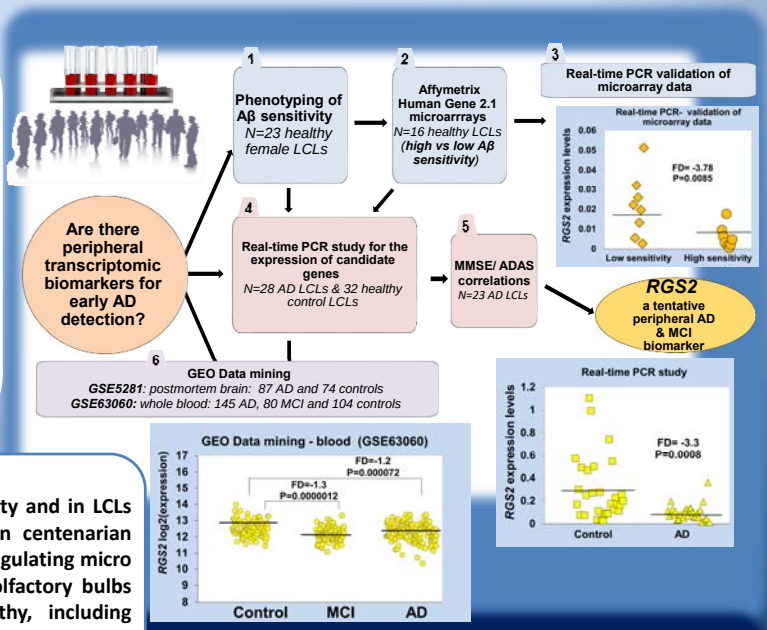
Methods

Genome-wide transcriptomics of LCLs from healthy individuals and AD patients for searching gene expression levels that are correlated with in-vitro Aβ sensitivity. Bioinformatic data mining of published transcriptomic datasets validated our findings in AD patients and MCI individual's blood samples.

Next, we explored the LCLs gene expression profiles of centenarians along with AD patients.

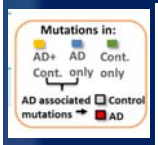
Postmortem olfactory bulb cDNA samples (19 AD, 20 controls) were subjected to RNA-Seq. We corroborated RNA-seq data results in terms of mutation analysis.

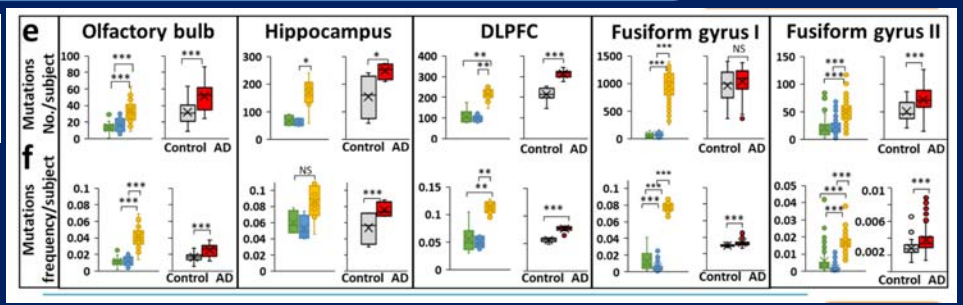
Lastly, we employed public RNA-seq data-mining focusing on mutation analysis of postmortem hippocampus, dorsolateral prefrontal cortex, fusiform gyrus and superior frontal gyrus (N=583).

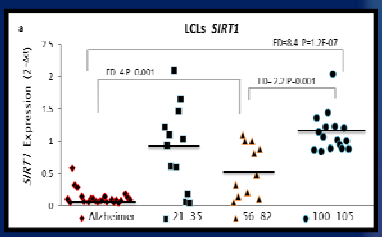


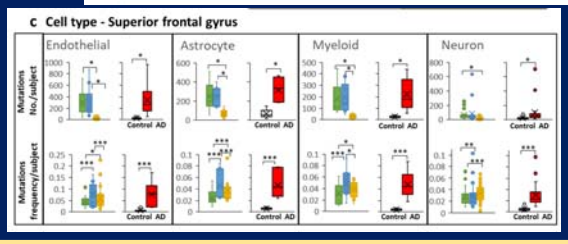
Results

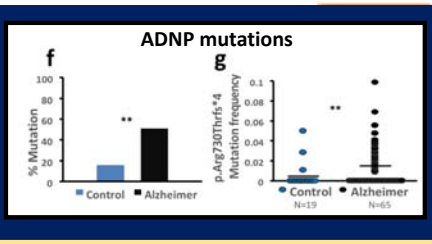
***RGS2* expression levels were lower in LCLs exhibiting higher Aβ sensitivity and in LCLs from AD patients. *SIRT1* expression levels were significantly higher in centenarian compared with AD LCLs, while the opposite was observed for the *SIRT1* regulating micro RNA species, miR-132 and miR-212. RNA sequencing of postmortem olfactory bulbs revealed somatic aging/AD-linked mutations converging on tauopathy, including mutations in *ADNP*.**

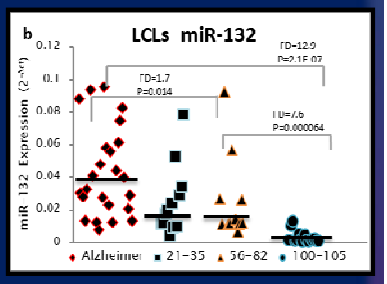












Conclusion: **Taken together, our results demonstrate an additional complexity of sporadic AD, already recognized as a multifactorial disease. The transcriptional changes could take part in neuroprotection, while subsequent with somatic mutations accumulation lead to further neuronal damage.**

Selected references:

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3] Ivashko-Pachima Y*, Hadar A*, Grigg I, Korenková V, Kapitansky O, Karmon G, Gershovits M, Sayas CL, Kooy RF, Attems J, Gurwitz D, **Gozes I**. Discovery of autism/intellectual disability somatic mutations in Alzheimer's brains: mutated ADNP cytoskeletal impairments and repair as a case study. Mol Psychiatry. 2019 Oct 30. ***Equal contribution**.