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Case Report

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Gene Expression Changes in the Human Brain Upon Aging

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ABSTRACT

Aging is common to all living organisms including human. Very few studies so far focused on RNA expression changes in the human brain upon aging. In particular, I have analysed neuronal and glial cell type marker genes for differential expression based on exon microarray data from overall 1,234 post-mortem individual brain samples (ages 16 to over 100) and 10 brain regions. I also quantified neurons and oligodendrocytes using high resolution imaging and machine learning analyses. My study yielded insights into cell type specific gene expression changes in aging in the human brain.

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Abbreviations

HCL: Hierarchical Classification

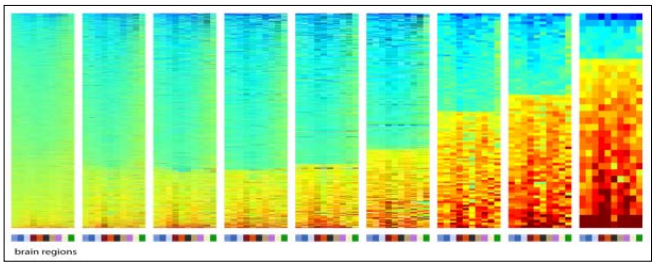
T-SNE: T-Distributed Stochastic Neighbour Embedding

Introduction

The world human population is increasingly aging. We can extend the lifespan of model organisms (such as mice, c. elegans, drosophila) by up to 100 fold (e.g through dietary restrictions, targeted gene intervention or sports activity) but we still do not know how to significantly extend human lifespan [1]. In terms of molecular pathways, genomic instability, cellular attrition, loss of proteostasis, stem cell exhaustion telomere attrition mitochondrial dysfunction and cellular senescence as well as epigenetic alterations were linked to aging So far, mutations in several genes have been linked to Aging (e.g Age1) [2]. But still many other genes (as well as molecular pathways) are still to be found as linked to aging.

Summary

The advantage of exon microarrays is that these allow analysis of both gene expression changes and alternative splicing. I also conducted alternative splicing analyses on the young and old brain samples data (yet unpublished data). In particular, I used Matlab and AltAnalyze software (http://www.altanalyze.org/) for the analysis. I applied statistical test and classification methods (e.g. T-SNE) on the data. For the imaged data I used machine learning targeted Matlab tools. I have detected 9 genes that were significantly altered in all the 10 analysed brain regions (including one long non coding RNA). I applied hierarchical classification (HCL) on lists of genes that were commonly altered in up to 10 brain regions (see figure 1). I also ran statistical correlation analyses on the data. I also compared the UK consortium brain expression (UKBEC) data to 134 3' arrays expression data from the north American brain bank (NABEC) on 2 brain regions (frontal cortex and cerebellum). I also downloaded 7 brain cell type mouse RNA-Seq database (the Allen brain atlas) for the comparative analyses of 7 different neuronal/glial cell types [3]. For follow up, I conducted gene expression and classification analyses on young and old microglia depleted and repopulated mice [4]. I found several common genes that were altered in both young vs old mice and human samples. I then downloaded and classified expression data from the human illumine body map (e.g thyroid, white blood cells). Furthermore, by application of linear regression on neuronal and microglial cell types I was able to predict the samples biological age in high accuracy.



Legend

Hierarchical classification on genes that were detected as commonly altered in up to 10 brain regions concurrently (blue, down regulation, red – up, bottom bar – the brain regions).

Conclusions

A better understanding of aging will allow us to develop diagnosis methods for premature aging. In the future, application of single cell RNA sequencing will allow even better analysis. Additionally, the data may be compared to expression data from aging mice models.

Ethics Approval

All the samples had Ethics approval (MTA: university of Edenborough).

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Conflict of Interest
The author declares no conflict of interest.

Author Contributions
L.S analysed the described data and wrote this paper.

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