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Opinion

Alternative Splicing Changes in Human Aging Brain Samples

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Abstract

Alternative splicing affects differential isoform generation from genes and may also affect the protein products cellular function. Targeted splicing analysis of exon array analysis of young compared to middle and old post mortem brain samples from 1,234 samples (a total of 10 brain regions) aged from 16 to over 100 allowed me to detect significant alternative splicing changes upon human aging. This kind of data may allow us to better understand the underlying molecular mechanisms.

Key words: giant intracranial aneurysm; bypass; trapping; pediatric neurosurgery

Introduction

Aging is common to all human organisms. I have analysed exon array data (samples were collected by the UK brain bank, UKBEC [1]) focusing on alternative splicing.

Summary

So far alternative splicing was hardly analyzed in human post mortem brain data. I conducted widespread Alternative splicing analysis on human exon array data produced from the UKBEC consortium post-mortem brain samples. I used AltAnalyze software (www.altanalyze.org). Prior to the alternative splicing analysis I applied differential expression analysis on the samples and compared between genes commonly altered between the different brain regions. For the alternative splicing analysis I computed splicing index (SI) followed by linear regression. Overall, 3,522 Ensemble transcripts were found as significantly altered in the substantia nigra (SNIG) brain region in young vs old samples (see supporting table 1 which included the relevant exons, regulation direction, junction p-value, gene symbol, adjusted p-value, functional relevance, splicing index, constitutive/alternative exon information, baseline probe-set expression, exon annotation, exon annotation, exon region and junction location). I then searched for functional protein motif domains (ST2) including z-score, permutation and adjusted p-value and relevant gene symbols. Linear regression analysis detected exon inclusion events in young vs old samples in SNIG (ST3), exon inclusion results (ST4). Notably, microRNA z-scores were also calculated (ST5). 570 of 907 analysed miRNAs had significant permute p-value.

Conclusions

A better understanding of human brain aging, and in particular of the underlying alternative splicing changes will allow us to develop early 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. Also, regulation by microRNA and protein domains of the alternative spliced produced may also be analysed.

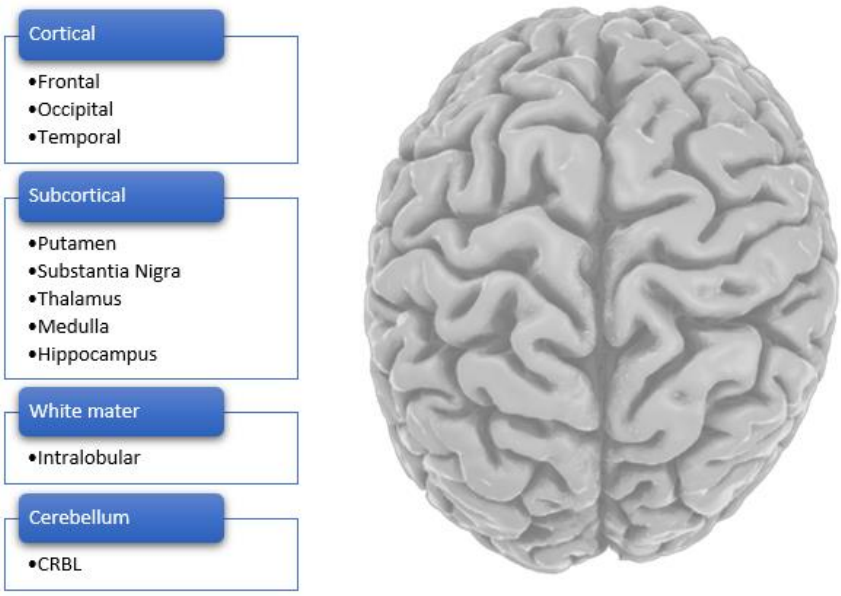

Figure 1: The 10 analyses brain regions (UKBEC exon array dataset)

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Abbreviations

HCL - Hierarchical classification.

SNIG - Substantia nigra.

t-sne - t-distributed stochastic neighbour embedding.

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

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