Linking Human Brain Development and Synaptic Plasticity to Alternative Splicing

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Abstract— **In this research, we studied the spatial and temporal implications of alternative splicing (a mechanism that allows single genes to code for multiple proteins) in the human brain, especially in regards to synaptic plasticity (the ability of neurons to strengthen or weaken in response to stimuli). We concluded that alternative splicing varies meaningfully throughout the human lifespan. Peaks in splicing are observed during childhood and late adulthood. We demonstrated that highly spliced genes during childhood are significantly associated with nervous system development and synaptic plasticity, while highly spliced genes in late adulthood are associated with neuronal degeneration and age related neurological diseases. This research also revealed that genes associated with synaptic plasticity showed significantly higher splicing than the other genes. Finally, we were able to predict, with greater than 95% accuracy, brain region and development stages using only the splicing characteristics of plasticity genes.**

I. MATERIALS

We used microarray expression data from the series GSE25219 of the Gene Expression Omnibus (GEO) database uploaded by Kang et al. [1]. The database used the *Affymetrix Human Exon 1.0 ST Array* platform to collect exon expression for 1114 brain samples spanning across different brain regions, age groups and ethnicities. We used R language and the packages available in R to perform alternative splicing and differential splicing analysis. The Ingenuity Pathway Analysis (IPA™) tool was used for gene ontology analysis.

II. METHODS

Finding Isoforms from Robust Multichip Analysis (FIRMA) method was used to quantify alternative splicing from exon level expression due to its robustness in the presence of chip and probe level noise [2]. We grouped FIRMA scores by age group and did correlation analysis to find similarities across age groups. We further used differential splicing analysis to find differentially spliced genes in each age group (pre-natal, childhood, adulthood and late adulthood). Gene ontology analysis was performed to find the molecular/biological and cellular functions that are regulated by these differentially spliced genes. Alternative splicing of synaptic plasticity-related genes was also studied.

III. RESULTS

Alternative splicing increases significantly from infancy to childhood and from adulthood to late adulthood (Figure 1). Differential splicing analysis yielded a list of 2044 genes that are highly spliced in childhood compared to infancy and a list of 682 genes that are highly spliced in late adulthood compared to adulthood. Functional analysis showed that all of the highly spliced genes in late adulthood were associated with neuro-degenerative (like Parkinson's and Alzheimer's) and other diseases associated with late adulthood. Similar analysis on the highly spliced genes in childhood revealed that they were associated with neuronal development and signaling. We also found that synaptic plasticity genes are significantly more spliced ($p < 0.05$ with two-tailed t-test) than other genes and their splicing characteristics vary in different brain regions.

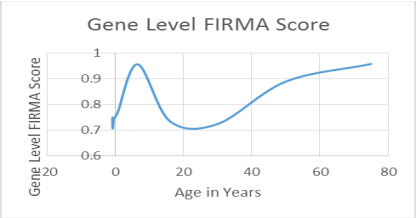

Figure 1. Alternative Splicing Score (FIRMA score) as a function of age.

IV. CONCLUSIONS

This research demonstrates that understanding alternative splicing in the human brain is critical to achieving a complete picture of brain development. All major brain regions and periods were shown to have unique splicing patterns that may be the root cause of their differentiation. These splicing patterns were able to differentiate different regions of the brain better than the gene expression patterns. While differentially spliced genes in adulthood are distributed broadly across the functional landscape, during childhood and late adulthood periods, they are significantly concentrated in specific pathways relevant to processes (neuronal development and signaling) and diseases associated with that age. While plasticity genes have similar alternative splicing variations across the development stages, they have higher splicing than other expressed genes – indicating that genes regulating synaptic plasticity and memory formation demand more protein isoforms. This research has implications for epigenetics, research on neurological diseases and tissue grading. It shows that in many instances alternative splicing is an insightful gauge of human brain development.

REFERENCES

[1] Kang, Hyo Jung, et al. "Spatio-temporal transcriptome of the human brain."*Nature* 478.7370 (2011): 483-489.

[2] H. Purdom, E., et al. "FIRMA: a method for detection of alternative splicing from exon array data." *Bioinformatics* 24.15 (2008): 1707-1714.New York: Springer-Verlag, 1985, ch. 4.