

Linkage of alternatively spliced exons proliferates in neuronal genes

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Based on publicly available RNA-seq data of human hippocampus samples, we identified alternatively spliced (AS) exons genome wide along with assessing the genes percentage spliced in (psi) values. The data has been compiled on more than 30 samples for each gene. Along with psi values we compiled pairwise covariation matrix across all AS (exon skipping) exons based on Pearson r^2 . Further Agglomerative Hierarchical Clustering (AHC) procedure on matrix revealed dense AS exons clusters with linked exons, with clusters size in the interval of [2...19] (pairwise correlation p -value < 1E-6). There were around 2,200 genes with clusters of coordinated AS exons.

Further analysis revealed AS clusters maintain antagonistic or independent relations within a gene. We explored the traits of genes abundant with AS clusters: the majority proved to be neurospecific genes, including synapse, and cytoskeletal (axonal) genes. Notably, Neurospecific splice factors (SFs) also maintain expanded coordinated AS regulation.

While the previous study observed coordinated splicing before [1], the scale of the phenomenon has not been explicitly highlighted. From the evolutionary point of view, and, given the information complexity of splicing decreases upon exon co-variation, we may speculate that the rapid response to the homeostatic environment favors quick coordinated splicing mediated tune-up of the gene's isoform. Still, the mechanistic background of phenomenon is not elucidated. One of the viable hypothesis is the specific secondary structure of mRNA favoring the quick coordinated SFs binding.

In our report we address the phenomenon and consider several examples of coordinated AS.

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References

1. Fagnani M. et al. Functional coordination of alternative splicing in the mammalian central nervous system. *Genome Biol.* 2007;8(6):R108