

## Conserved age-related splicing regulation in primate brains.

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Alternative splicing (AS) is the process that allows single gene to produce several mRNA (and consequently proteins) through differential exclusion of introns. AS is known to be very abundant in higher eucariotes and affects in human up to 95% of genes. Recently, AS levels were compared across the set of tissues in several species. Results show that while inter-species differences are the main factor of splicing variability, sufficient proportion of splicing events exhibit prominent conservation of tissue specific splicing patterns across all mammals [1,2]. While these studies are the important step toward understanding of the splicing evolution and regulation, the analysis done was restricted to small amount of genes with unambiguous orthologs in all animals studied.

Here we made polyA RNA-seq for 174 brain samples (from prefrontal cortex) from more than 100 individuals of three species (human, chimpanzee and rhesus monkey) of different ages (from newborn to old) resulted in 2.7 billions reads. We used these data to create unbiased, not-human-based annotation for all three genomes, that allow us to perform the genome wide comparative analysis of species-related and age-related alternative splicing variability in higher primate brains for the first time.

In agreement with previous studies, our results show that inter-species differences are the main source in the splicing variability in our data. Up to 45% (3335) of the expressed genes have significant inter-species differences in splicing, up to 20% of them can be explained by single nucleotide substitutions in the corresponding splicing sites. We have shown that 23% (1711) of the expressed genes change splicing with age in at least one species. In contrast to the inter-species differences, the age-related regulation of the alternative splicing of coding exons exhibit striking conservation among the studied species. We have found prominent enrichment in functions linked to the neuronal development and synapse formation among the genes with age-related splicing changes. Our analysis shown significantly higher sequence conservation of the age-related exons, as well as their flanking regions, in the whole primate lineage, than expected by chance.

The frequency of the intron retention changes with age in 16% of genes. Interestingly, there are about two-fold more age-related retained introns in human, than in the other species. Intron retention is more abundant in newborns and drops with age. We shown that the frequency of intron retention does anti-correlate with the gene expression level, and that age-related retained introns meet frequently near 3' end of genes, and significantly higher proportion of them are the last introns. These observations point to possible participation of the retained introns in the age-related gene expression regulation.

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