HEALTH RESEARCH ABSTRACT SUBMISSIONS #8

Name *	Shihao Shen
Email *	shihao-shen@uiowa.edu
Educational Level *	PhD Candidate
If Selected Other	
College *	College of Public Health
Department *	Biostatistics
Title of Research *	Evolution of alternative splicing in primate brain transcriptomes
Other Authors *	Lan Lin, Post-Doc (UI College of Medicine); Peng Jiang, Post-Doc (UI College of Medicine); Seiko Sato, Technician (UI College of Medicine); Beverly L. Davidson, PhD (UI College of Medicine); Yi Xing, PhD (UI College of Medicine)
Introduction & Purpose *	Alternative splicing is a predominant form of gene regulation in higher eukaryotes. The evolution of alternative splicing provides an important mechanism for the acquisition of novel gene functions. In this work, we carried out a genome-wide phylogenetic survey of lineage-specific splicing patterns in the primate brain, via high-density exon junction array profiling of brain transcriptomes of humans, chimpanzees and rhesus macaques.
Experimental Design *	RNAs from cerebellum of six chimpanzees, six rhesus macaques and two pooled human cerebellum samples were hybridized to the Affymetrix Human Exon Junction Array (HJAY). We used all HJAY probes that perfectly matched orthologous transcripts from chimpanzee and rhesus macaques for comparative analysis.

Results *

We identified 509 genes showing splicing differences among these species. RT-PCR analysis of 40 exons confirmed the predicted splicing evolution of 33 exons. Of these 33 exons, outgroup analysis using rhesus macaques confirmed 13 exons with human-specific increase or decrease in transcript inclusion levels after humans diverged from chimpanzees. Some of the human-specific brain splicing patterns modulate key protein-protein interactions, and some affect genes previously implicated in brain diseases. Strikingly, for exons showing splicing differences across species, we observed a significant increase in the rate of silent substitutions within exons, coupled with accelerated sequence divergence in flanking introns. This indicates that evolution of cis-regulatory signals is a major contributor to the emergence of human-specific splicing patterns.

Conclusions *	Together, our data reveal widespread human-specific changes of alternative splicing in the brain, and suggest an important role of splicing in the evolution of neuronal functions and associated diseases.

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