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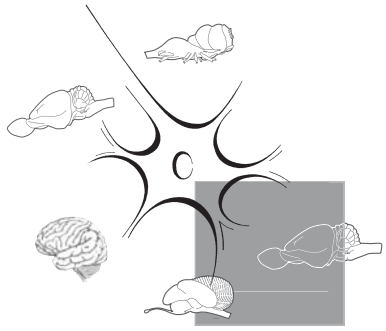

The Fetal Brain Provides a Raison d'être for the Evolution of New Human Genes

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The genome revolution that included sequencing of the human and chimpanzee genomes promised to provide answers to how humans evolved their unique cognitive abilities. However, comparisons at the DNA level in protein-coding regions of the genome among primates have revealed few clues as to the molecular mechanisms underlying human brain evolution. As previously predicted [King and Wilson, 1975], we are therefore left with differential regulation of gene expression in the human lineage as a potential major evolutionary force driving human cognition. The recent advent of microarrays and next generation sequencing technologies have allowed us to compare gene expression in the brains of humans and other species at a genome-wide level [Konopka and Geschwind, 2010]. However, the identification of a few hundred genes differentially expressed between human and non-human primate brain [Caceres et al., 2003] is unlikely in itself to explain the higher cognition in humans. In addition, gene expression in the human brain has been found to be the most evolutionarily constrained compared to other tissues [Wang et al., 2007; Brawand et al., 2011], consistent with investigations into evidence for accelerated evolution among human brain genes coming up empty handed [Konopka and Geschwind, 2010]. Therefore, the contribution of potential genomic mechanisms to human brain uniqueness still remains mostly unknown.

In a recent report, Zhang et al. [2011] attempted to address this feature of human brain evolution by examining the role of genes expressed in the fetal human brain. Until the recent availability of gene expression datasets from human fetal brain, all studies of genomics within the human brain have utilized adult tissue samples. Since the period of prenatal development is critical for normal cognitive functioning (as evidenced by the existence of numerous neurodevelopmental disorders like autism), analysis of fetal brain gene expression should likely provide key insights into human cognition where adult gene expression falls short. Zhang et al. [2011] used a combination of published microarray data, unpublished RNA sequencing data, and expressed sequence tag data in their analyses. They focused specifically on what they call 'young' genes, or those genes that have arisen in the primate lineage. By highlighting the young genes in the transcriptome data, the authors uncovered important results regarding human brain evolution.

Zhang et al. [2011] reported that in humans young genes are enriched among brain-expressed genes and up-regulated early in brain development. Interestingly, there was an abundance of transcription factors among the young genes [Zhang et al., 2011]. This acceleration of *trans*-activators of expression could potentially have allowed for a faster means of altering gene expression networks in the human brain rather than the potentially slower modification of *cis*-activators (such as promoters) on a gene-by-gene basis. These findings are congruent with other work finding a similar effect of faster evolution of *trans*-activators (i.e. microRNAs) on human brain gene expression [Somel et al., 2011], as well as the finding that the human form of *FOXP2*, a developmentally expressed transcription factor important for language that has undergone accelerated evolution, has unique transcriptional targets [Konopka et al., 2009]. Together, these data support the hypothesis that human-specific regulation of gene expression has been more critical for the development of human cognition than an overall accelerated evolution of protein-coding genes expressed in the brain.

The authors also discovered that young genes are up-regulated in the neocortex

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compared to non-cortical areas in humans [Zhang et al., 2011]. This finding again makes sense in light of recent studies showing an increase in developmental remodeling of gene expression in the human prefrontal cortex compared to the cerebellum [Somel et al., 2011]. Zhang et al. [2011] attributed the increase in new genes in the neocortex to a correlation with the evolutionary origin of the neocortex: only the genes that evolved after the common ancestor of tetrapods and fish are enriched in the neocortex. Taken together with their finding of enrichment of young genes in the brain, these data suggest that the origination of new genes in the human lineage contributed to the evolution and development of this new brain region.

Another important and novel finding from this study is that young genes enriched in the human fetal brain evolved significantly faster than old genes [Zhang et al., 2011]. Interestingly, many of these young genes identified as either under positive selection or to be human specific are poorly characterized. Therefore, it is possible that these genes are enriched for specific ontologies or functions that are either novel or specific to the developing human brain. In addition, these data prioritize genes for further analysis, especially in the context of neurodevelopmental disorders. Animal models, such as making 'humanized' transgenic mice, could provide important insights into the functions of these genes.

One caveat to this study is the use of mouse expression data for comparison to the human gene expression data. Therefore, it is possible that some of the findings are not human specific, but rather can be attributed to the primate lineage in general. Unfortunately, non-human primate fetal brain expression data are not currently nor likely to become available. However, the generation and use of any other mammalian developmental dataset could certainly increase our understanding of the phylogeny of these genomic features.

The inclusion of gene expression data from developing human brain was critical for the study by Zhang et al. [2011], as similar analyses in adult human brain did not find evidence for accelerated evolution [Wang et al., 2007; Konopka and Geschwind, 2010]. Two other recent papers have demonstrated how developmental trajectories lead to important changes in human brain gene expression patterns [Colantuoni et al., 2011; Kang et al., 2011], and provide, for the first time, gene expression data in the human brain throughout the entire lifespan, including fetal development. It will be exciting for these datasets to be queried in a similar manner to provide validation to these results. In addition, with these expanded datasets it will be interesting to determine whether genes with significant expression patterns during fetal development have undergone faster evolution overall rather than just the young genes among them. The findings by Zhang et al. [2011] are an important first step for in-depth analyses on a genome-wide scale of the contribution of developmentally expressed genes to human brain evolution.

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