Transcription factor networks play a key role in human brain evolution and disorders

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Although the human brain has been studied over past decades at morphological and histological levels, much remains unknown about its molecular and genetic mechanisms.

Furthermore, when compared with our closest relative the chimpanzee, the human brain strikingly shows great morphological changes that have been often associated with our cognitive specializations and skills.

Nevertheless, such drastic changes in the human brain may have arisen not only through morphological changes but also through changes in the expression levels of genes and transcripts.

Gene regulatory networks are complex and large-scale sets of protein interactions that play a fundamental role at the core of cellular and tissue functions. Among the most important players of such regulatory networks are transcription factors (TFs) and the transcriptional circuitries in which TFs are the central nodes.

Over past decades, several studies have focused on the functional characterization of brain-specific TFs, highlighting their pathways, interactions, and target genes implicated in brain development and often disorders. However, one of the main limitations of such studies is the data collection which is generally based on an individual experiment using a single TF.

To understand how TFs might contribute to such human-specific cognitive abilities, it is necessary to integrate the TFs into a system level network to emphasize their potential pathways and circuitry.

This thesis proceeds with a novel co-expression network approach to infer the evolution of these networks. Using human, chimpanzee, and rhesus macaque, we spanned circa 35 million years of evolution to infer ancestral TF networks and the TF-TF interactions that are conserved or shared in important brain regions.

Additionally, we developed a novel method to integrate multiple TF co-expression networks derived from human frontal lobe next-generation sequencing data into a high confidence consensus network. In this study, we also integrated a manually curated list of TFs important for brain function and disorders. Interestingly, such “Brain-TFs” are important hubs of the consensus network, emphasizing their biological role in TF circuitry in the human frontal lobe.

This thesis describes two major studies in which DNA microarray and RNA-sequencing (RNA-seq) datasets have been mined, directing the TFs and their potential target genes into co-expression networks in human and non-human primate brain genome-wide expression datasets.

In a third study we functionally characterized *ZEB2*, a TF implicated in brain development and linked with Mowat-Wilson syndrome, using human, chimpanzee, and orangutan cell lines. This work introduces not only an accurate analysis of *ZEB2* targets, but also an analysis of the evolution of *ZEB2* binding sites and the regulatory network controlled by *ZEB2* in great apes, spanning circa 16 million years of evolution.

In summary, those studies demonstrated the critical role of TFs on the gene regulatory networks of human frontal lobe evolution and functions, emphasizing the potential relationships between TF circuitries and such cognitive skills that make humans unique.