GENETIC NETWORKS UNDER HUMAN-SPECIFIC REGULATION REVEALS CLUES ABOUT THE EVOLUTION OF THE MODERN LANGUAGE-READY BRAIN

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1. Introduction

Since the discovery of FOXP2 (Fisher & Vernes, 2015), the field of the genetics of language has acknowledged that to understand the genetic background of the faculty of language we have to shed light on the genetics of its cognitive subcomponents first. In addition, we now have the unprecedented opportunity to be able to work not only with data from other non-human species, but with that of our own closest extinct relatives, the Neanderthals and Denisovans (Pääbo, 2014), as well as an ever-growing corpus of genomic information from modern human populations. However, the challenge presented by this wealth of data is to structure knowledge in the form of testable hypotheses bridging genotype and phenotype.

We propose that perturbations in the background genomic networks of modern humans, in the form of various neurodevelopmental disorders, constitute a key step in understanding the complex interactions between different levels of analysis (genome, protein, cell, system). Crucially, this data is necessary to accurately inform us about our evolution as a species in general and the emergence of the faculty of language in particular. We present here an innovative approach that takes advantage of a database of high-frequency *Homo sapiens*-specific genetic variation in modern populations (Kuhlwilm & Boeckx, 2019) to experimentally test how gene expression programs key for brain development are influenced by human-specific signatures of regulation. We focus particularly on the often overlooked role of enhancers, promoters, the 5'/3' UTRome and cis-eQTLs (allele-specific expression level changes) affecting brain growth trajectories.

2. Results

In our studies we take as our starting point an extended paleogenetic dataset (Kuhlwilm & Boeckx, 2019) to evaluate how genetic regulation affects the ex-

pression of genes in the developing human brain, and pursue a multi-leveled evo-devo approach. Our first step focuses on the role of those enhancers and promoters, which determine when and where the genes are expressed, harboring human-specific single-nucleotide changes. The network of genes controlled by such regulatory regions are then evaluated at the cell level, where single-cell gene expression data analysis reveals genetic networks relevant for the generation and proliferation of progenitor cells in the developing cortex. The second step of this study assesses quantitatively the impact of human-specific single nucleotide changes on gene expression through a single-tissue eQTL analysis in 13 different brain tissues. In this analysis, we assess the effects of modern-specific variants in gene expression levels in the brain. These cis-eQTLs significantly overlap ($p = 0.0075$) with a *Homo sapiens* positive selection study. Overall, results pointing to genes implicated in neurodevelopment and clinical conditions (such as macrocephaly and microcephaly, developmental language impairment or various syndromes) stand out. The results of these two studies are complemented by the picture offered by 5'/3' untranslated regions that also underwent changes in modern human evolution.

The resulting comprehensive network we arrive at enables us to align genes implicated in neurodevelopmental disorders with distinct cognitive phenotypes in a way that candidate gene studies does not allow. This mosaic of interacting genetic nodes helps us elucidate the ontogeny of cognitive sub-systems that underlie the faculty of language, bridging genotype and phenotype, and providing candidate molecular pathways for experimental validation.

References

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