Proyecto PID2019-104700GA-I00 financiado por MCIN/ AEI /10.13039/501100011033

Identificación del proyecto:

Taxonomía de la unión de factores de transcripción en el genoma completo de primates para el estudio de especializaciones del cerebro humano en salud y en enfermedad

Descripción del proyecto:

Humans possess a nervous system which confers very distinct cognitive abilities and very distinct cognitive disorders. The study of brain development is critical for the understanding of the evolution of these distinct features. To discern the genetic causes in evolution and disease influencing human-specific phenotypes, one needs to identify the relevant variants affecting relevant genes among thousands of other variants predicted to be neutral. Among the approximately 35 million single nucleotide polymorphisms (SNPs), 5 million insertions or deletions (indels), and 90 megabases of structural variants where the human and chimpanzee genomes differ are countless variants associated with development, function or disease. However, identifying these rare variants from among the thousands of variants expected to be neutral is a herculean task, a truly needle-in-a-haystack scenario. We and others have reasoned that identifying evolutionarily relevant genetic variants, as well as those implicated in disease or function, can be guided by the analysis of species differences in intermediate molecular phenotypes (e.g., transcriptomic and epigenomic signatures), which are most likely the primary effects of genomic variation. But even when the connection has strong probability of causality, one still needs to demonstrate the mechanisms underlying the phenotypic change, which is an effort rarely pursued by evolutionary biologists. This project aims to deal with these two problems by i) reduce the search space for relevant variants into a tractable list, and ii) test their functional effects in a system proximal to human fetal brain development consisting in iPSC-derived neural cultures.

This project goes one step further in its strategy to identify evolutionarily relevant variants, as it directly interrogates divergence in the segments of the predicted regulatory elements that are directly functionally affecting gene expression: the transcription factor binding sites (TFBS). The study of the brain spatiotemporal convergence of risk for multiple neuropsychiatric traits has pointed to a reduced number of transcription factors with critical involvement in normal neurodevelopment. This project aims to dissect the temporal dynamics of genomewide transcription factor binding site occupancy for a selection of risk convergence transcription factors (TF) at different stages of neurodevelopment and with an evolutionary perspective. In particular, we will i) compare TF binding sites in neural cultures derived from iPSC in humans, chimpanzee and macaques, ii) integrate multiOMICs comparative datasets of RNA-seq, ChIP-

seq and Hi-C to link divergent binding sites to gene expression and iii) associate those changes to human specific variants. This framework will provide the means to prioritize evolutionary relevant variants for human-specializations and to be tested in a CRISPR/Cas9 iPSC system for phenotypic characterization.

Financiación: AGENCIA ESTATAL DE INVESTIGACION

154.880,00€