Proyecto PID2022-140137NB-I00 financiado por MCIN/AEI/10.13039/501100011033/ y por FEDER Una manera de hacer Europa

Identificación del proyecto:

Comprender la evolución de las redes reguladoras controladas por factores de transcripción bHLH para identificar bases genéticas de rasgos derivados del neurodesarrollo humano

Descripción del proyecto:

The confluence of recent technological advances in the fields of brain organoids and single-cell genomics, coupled with improved primate genome assemblies and annotations, allows for the first time to efficiently probe an old conundrum: what are the specific genetic variants responsible for human brain specializations and human-derived brain disorders among the millions of divergent positions separating humans from chimpanzees. Single-cell integrative functional analyses performed in recent years have greatly expanded our knowledge of the molecular logic of human cortical development. In addition, large-scale spatiotemporal expression and epigenomic maps of the brain across the human lifespan have allowed the cellular and temporal localization of neuropsychiatric risk. However, while GWAS and comparative transcriptomic and epigenomic analyses have identified putative evolutionary and disease relevant regulatory regions, the search space, and uncertainties about the modes of regulatory evolution and disease risk are still overwhelming. In this proposal we focus on certain members of the basic helix-loop-helix (bHLH) family of transcription factors (TFs), which are critical for the normal development of cortical excitatory neurons and are proposed to be major players in chromatin remodeling during neuronal differentiation. Since this group of TFs acts upstream of several master TFs that determine neuronal identity between cortical layers and axon guidance, we reasoned that assessing functional divergence in their experimentally determined binding sites would lead us to meaningful insights into their contribution to disease risk and human derived traits. We will use an innovative combination of techniques to identify and assess the impact of gains and losses of bHLH binding sites, including CUT&TAG on human and non-human great ape iPSC derived neurons (including composite allo-tetraploid cell lines), multiple types of bioinformatic analysis and CRISPR/Cas9 candidate validation in human brain organoids. This basic-research proposal aims to bridge the gap between the fields of neurodevelopment and evolutionary biology and, in addition to providing relevant insights into fundamental aspects of human-derived neurodevelopment, it is expected to be a proof of concept for a new methodological framework to study the evolution of gene-regulatory networks.

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300.000,00€

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