December 12th 2023 | 4:00 PM CET VIRTUAL

iPSZÜRICH

A Lecture Series Focused on Induced Pluripotent Stem Cells

Radboud Universiteit

DONDERS INSTITUTE

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LEVERAGING HUMAN NEURONAL NETWORKS ON MICRO-ELECTRODE ARRAYS TO STUDY DISEASE-SPECIFIC GENOTYPE-PHENOTYPE CORRELATIONS

Despite considerable progress in elucidating the genetic architecture of neurodevelopmental disorders (NDD), including intellectual disability (ID) and autism spectrum disorders (ASD), a major gap exists between the genetic findings and deciphering the cellular or molecular pathobiology of NDDs. In particular, understanding which gene expression changes in specific cell types have the most relevant functional consequences, and whether or not those consequences overlap in different patients. I will discuss our recent approaches to link changes in neuronal network activity in patient derived neuronal network to cellular and molecular pathways. To this end we generated neuronal networks from multiple patient-derived neurons with mutations in 14 different NDD genes. We monitored the spontaneous activity of neuronal networks coupled to micro-electrode arrays (MEAs) over time and compared their activity to healthy controls and between NDDs. Using independent clustering analysis, encompassing independent MEA parameters, we show that all patient lines deviated from healthy control lines and their respective isogenic lines. We show that neuronal networks with mutations in the same gene, including the isogenic lines, functionally clustered together. At the same time, we show that subtypes of NDDs sharply segregated from each other with distinguishable network patterns. The most pronounced differences between NDDs were observed at the level of spontaneous network activity, either at the level of network burst frequency, or network burst length. Finally, by combining MEA recordings with transcriptomics within the same experiment (MEA-Seq) we identified molecular pathways that underlie specific neuronal network phenotypes observed in NDD subtypes. Our data indicate that MEASeq is a robust and sensitive method to perform genotype-phenotype analyses, which can serve as a powerful platform to identify functional points of convergence between ASD genes and be used for high-throughput drug screening assays.