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Modelling neuro developmental disorders in a dish

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The leading manifestation of brain dysfunction is intellectual disability, affecting approximately 3% of the general population. Given the uniqueness and the complexity of human cognition and behavior, studies in humans are essential to understand the role of the multitude of genes involved in these processes. We previously developed IPSC from patients with *MECP2* duplication syndrome carrying different duplication sizes, to study the impact of increased *MePC2* dosage in human neurons. *MECP2* duplication syndrome is a severe neurodevelopmental disorder in males, characterized by severe neurodevelopmental delay with onset at birth, limited or absent speech, hypotonia, epilepsy, autism and motor dysfunction. Cortical neurons derived from Mecp 2dup-iPSCs had more synapses and altered network synchronization as well as dendritic complexity. Next, we tested a series of epigenetic drugs for the ability to rescue neuronal defects and validated two HDAC inhibitors as potential clinical candidates. We are currently developing an iPSC model for a novel tubulinopathy, characterized by intellectual disability associated with characteristic dysmorphic signs: circumferential skin creases, cleft palate, facial dysmorphisms and short stature. This developmental disorder is caused by mutations in a novel gene, *MAPRE2* (Microtubule-Associated Protein Member 2) encoding a member of the EB family. We derived patient-specific induced Pluripotent Stem Cell (iPSC) and established isogenic rescue lines as well as patient specific knock-in lines using CRISPR/CAS9. These iPSC's are then differentiated towards Neural Progenitor Cells (NPC), cortical neurons and Cranial Neural Crest Cells (CNCC) using adapted and optimized differentiation protocols. Preliminary functional experiments using patient fibroblasts showed an increase in migration speed and overall mitosis duration. We will now perform similar experiments to analyze the mitosis and migration rate of iPSC derived NPC's and CNCC's. In addition a full morphological work-up is ongoing. We will present these novel data at the meeting.

Biography

Hilde Van Esch has completed her PhD from Katholieke Universiteit Leuven, Belgium. She has then pursued Post-doc at Institut Cochin in Paris on X-linked intellectual disability. She currently works as a Clinical Geneticist at the University Hospitals UZ Leuven and is Associate Professor in the Department of Human Genetics and Head of the Laboratory of Genetics of Cognition at the University of Leuven, Belgium. Her research interests includes the identification of genes involved in rare diseases and intellectual disability. She has published and co-authered more than 170 papers in reputed journals and is a Board Member of the European Society of Human Genetics.

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