UCDAVIS HEALTH | MIND INSTITUTE

2019-2020 Distinguished Lecturer Series
Bert DeVries, M.D., Ph.D.
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For more than 25 years the central theme of Bert de Vries research has been the clinical and molecular study of neurodevelopmental disorders such as intellectual disability and autism in order to increase insight in the aetiology of these common disorders. During his PhD project in the nineties at the Erasmus University Rotterdam, a large-scale clinical and molecular studies for the fragile X syndrome among 3500 mentally retarded individuals was performed. The fragile X syndrome is one of the syndromes in which autism plays a significant role.
He pioneered efficient and affordable methods for large scale detection of sub microscopic genome defects during his clinical fellowship period in 1999-2000 at The Institute of Child Health/Great Ormond Street Children's Hospital, London (Prof R. Winter), and continued at Dept. of Human Genetics, RUNMC, Nijmegen (Prof H.G. Brunner).
Since his start at the Radboud UMC in 2001, Bert de vries and his team have had a keen eye to select the right patients to delineate the genetic basis of intellectual disability and autism. One of the excellent textbook examples involves the elucidation of Koolen-de Vries syndrome, caused by a 17q21.31 microdeletion, and imminent haploinsufficiency of *KANSL1* residing within this genomic locus. Similarly, his clinical expertise in recognizing and selection of key patients has been instrumental in the discovery of the genes underlying Schinzel-Giedion syndrome, Bohring-Opitz syndrome, Cantu syndrome and *de novo* mutations in various genes underlying ID and autism. He facilitated the clinical interpretation of novel ID-related genes by using both functional and animal studies (such as for *TDP2*, *DEAF1* and *NR2F1*), as well as for genes related to autism (*ADNP, CHD8, DYRK1A*).
Importantly, the latter results were achieved by the international 'Microdeletion Network' under direct leadership of Dr. de Vries. Additionally, he has initiated the Human Disease Genes website series (http://humandiseasegenes.nl/), representing an international library of websites for professional information on genes and copy number variants and their clinical consequences.
Currently, he is focusing on 'quantitative facial phenotyping' and 'brain-on-dish' as novel tools for studying and diagnosing neurodevelopmental disorders.

Presentation Title: Genes for the Mind: What we can learn from Neurodevelopmental Disorders

The human brain is one of the most complex organs. Its normal development and function critically depend on proper and tightly regulated activity of a large number of genes. Neurodevelopmental disorders (NDD), such as intellectual disability (ID) and autism spectrum disorder (ASD), encompass a wide range of diseases that involve disruption of early neurobiological development. These disruptions cause developmental deviations which result in major impairments in cognition, communication, behavior and/or motor skills. NDDs are genetically and phenotypically highly heterogeneous and present a major challenge in medicine today. The prevalence of ID in developed countries is estimated to be 2%, of which the vast majority is expected to be caused by a defect of one of the genes involved in neurodevelopment. The paucity of disease relevant functional information limits clinical research and rational treatment of NDD. Furthermore, the identification of the aetiology of unsolved NDDs related to ID/ASD is still a challenge in clinical practice.

From an historical perspective, NDD were mostly identified based on additional clinical features such as facial recognition. Indeed, patients with a disease-causing mutation in the same gene often show remarkable similarity in their facial features despite being unrelated. For years, this phenomenon has been instrumental in the recognition of (novel) syndromes and this is still of utmost importance in today's clinical genetic practice; not only in ID/ASD patients with known disease-causing mutations are such facial dysmorphisms enriched, but also in ID/ASD patients with a candidate pathogenic genetic

variant. Despite the distinctive, yet sometimes subtle, facial features, phenotyping of patients (and parents) is currently a manual task, relying on clinicians' ability to recognize dysmorphism. The latter hampers large scale and objective characterization especially due to the rare occurrence of several novel ID/ASD syndromes of which a high proportion may not even be identified. So novel tools of quantitative facial phenotyping will open new windows for diagnosing of children with syndromic forms of ID/ASD.

From a genetic point of view, headway has been made by the recent introduction of whole genome sequencing (WGS), allowing the study of the entire human genome in a single experiment. Using WGS, we previously showed that 60% of patients with severe ID, as proxy for NDDs, can be explained by a *de novo* mutation affecting protein-coding sequence. Despite this success, WGS in our hands failed to identify clearly pathogenic non-coding mutations. Since then, little progress has been made in this field and the lack of large-scale studies reporting non-coding pathogenic mutations clearly illustrates that interpretation of genome variation outside of genes is still highly complex. This interpretation beyond the protein-coding sequence is today's toughest challenge in clinical genomics, but is of the essence to solve the so far 40% 'unsolved patients'.

For years, functional assessments of genetic variation for NDD in a patient-dependent manner were hampered by the inability to measure the effect in the affected tissue, e.g. the brain. With the upcoming of human induced Pluripotent Stem Cells (hiPSCs) technology these challenges have been overcome: patient-derived hiPSCs can now be derived from skin-fibroblast, or blood cells, and subsequently differentiated into neurons (iNeurons) to study the disease in a personalized manner. Multiple functional properties of these iNeurons – *or in fact, disturbances thereof* – can be measured, referred to as 'brain-on-a-chip' methodology.

During the lecture these innovative aspects will be addressed.