Board of examiners

Prof. Dr. Robert Hofstra
Department of Clinical Genetics
Erasmus University Medical Centre, Rotterdam, the Netherlands

Prof. Dr. Laurent Nguyen
Interdisciplinary Cluster for Applied Genoproteomics; GIGA-Neurosciences
University of Liège

Prof. Dr. Hilde Van Esch
Center for Human Genetics; Laboratories for Genetics of Cognition
UZ Leuven, KULeuven

Prof. Dr. Claudia Spits
Research Group Reproduction and Genetics
Vrije Universiteit Brussel

Prof. Dr. Ilse Smolders
Laboratory of Pharmaceutical Chemistry, Drug Analysis and Drug Information
Center for Neurosciences
Vrije Universiteit Brussel

Prof. Dr. Leonardus van Grunsven, Chair
Department of Cell Biology; Liver Cell Biology Laboratory
Vrije Universiteit Brussel

Prof. Dr. Anna Jansen, Promotor
Pediatric Neurology Unit UZ Brussel
Neurogenetics Research Group, Vrije Universiteit Brussel

Prof. Dr. Katrien Stouffs, **Promotor**
Centre for Medical Genetics, UZ Brussel
Research Group Reproduction and Genetics, Vrije Universiteit Brussel

Dr. Grazia Mancini, Co-promotor
Department of Clinical Genetics
Erasmus University Medical Centre, Rotterdam, the Netherlands

Dr. Ir. Alexander Gheldof, Co-promotor
Centre for Medical Genetics, UZ Brussel
Research Group Reproduction and Genetics, Vrije Universiteit Brussel

VRIJE UNIVERSITEIT BRUSSEL

PhD in Medical Sciences
2018-2019

INVITATION to the Public defence of

Laura VANDERVORE

To obtain the academic degree of **'DOCTOR OF MEDICAL SCIENCES'**

FUNCTIONAL CHARACTERIZATION OF GENES INVOLVED IN THE DEVELOPMENT OF THE HUMAN BRAIN.

Thursday, 12 September 2019 at 3 p.m.
In Auditorium **Piet Brouwer**
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussels

How to reach the campus Jette:
http://www.vub.ac.be/english/infoabout/campuses

Summary of the dissertation

This thesis studied the genetic causes and molecular mechanisms leading to malformations of cortical development (MCD), to enable a new gene-based MCD classification method, and to improve counselling and the diagnostic yield in clinic. First, mutations in genes (*COL3A1* and *ZIC1*) earlier described in other diseases were linked to cortical development. We identified bi-allelic *COL3A1* variants as novel genetic cause for cobblestone malformation and detected a novel dominant *ZIC1* variant leading to microcephaly and cerebellar malformations, hereby expanding the clinical phenotype previously associated with this gene (craniosynostosis).

Besides expansion of clinical phenotypes we studied the function(s) of Rotatin (*RTTN*) in cortical development in detail and made a revision of all clinical phenotypes in reported and novel cases (n=28). We found that *RTTN* mutants lack expression of Rotatin at the centrosome. This resulted in mitotic failure with centrosome amplification, multipolar cell division, aneuploidy and apoptosis in affected individuals, underlying the observed proliferation/apoptosis disorders (microcephaly and short stature). *RTTN* mutants also displayed structural or functional anomalies of ciliogenesis. Lastly, we show that RTTN localized at the centrosome in the leading edge of migrating iPSC derived neurons and colocalized with MYH10. This thesis also described a completely new gene *TMX2*, elucidated its function and showed the involvement of a novel protein family (PDIs) in MCDs. Bi-allelic *TMX2* variants led to microcephaly, polymicrogyria and drug-resistant epilepsy. *TMX2* mutants impaired protein folding, resulting in mitochondrial failure with decreased reserve capacity to account for oxidative stress. *TMX2* mutants dimerized, instead of staying in the monomeric form, mimicking the proteins' physiological response to oxidative stimuli.

Curriculum Vitae

Laura Vandervore was born on the 25th of August 1992 in Vilvoorde, Belgium. She studied Pharmaceutical Sciences at the Vrije Universiteit Brussel and obtained her master with great distinction in 2015. During her master thesis she studied potential biomarkers for real time pancreatic beta cell dead in type 1 Diabetes mellitus. After graduating, she joined the NEuroGEnetics (NEGE) research group as a PhD student at the Center of Medical Genetics (UZ Brussel) in October 2015. Here, she obtained a scholarship from the Marguerite-Marie Delacroix foundation, under supervision of Prof. Dr. Anna Jansen, Prof. Dr. Katrien Stouffs and Dr. Alexander Gheldof. One year later, she started a two-year international internship at the department of Clinical Genetics of the Erasmus Medical Center (Rotterdam, Netherlands) under supervision of Dr. Grazia Mancini. To enable this collaboration, she was granted travel funding of the FWO as well as support from the Neuro-MIG COST Action CA16118. Throughout her PhD training, she focused on molecular genetic diagnosis and functional characterization of genes in patients with malformations of cortical development. She has published three papers as a first-author, and a fourth is now under revision, and she co-authored four other papers. Her latest paper, published in Brain in April 2019, illustrated the functions of the *RTTN* gene in neuronal proliferation and migration and the implications of each different function during cortical development. In June 2018, Laura was awarded the Young Investigator Award for outstanding science by the European Society of Human Genetics. She was also privileged to chair the Neurogenetic and Psychiatric Disorders session at 52nd European Human Genetics Conference in Gothenburg, Sweden.