Expert center Nijmegen, The Netherlands: Kleefstra syndrome and EHMT1 gene

Core team: dr. Tijtske Kleefstra, dr. Nael Nadif Kasri, dr. Annette Schenck, Prof. Hans van Bokhoven

Many others involved (current actively studying):
Dr. Karlijn Vermeulen, MD PhD, child and adolescent psychiatrist
Dr. Ilse vd Werf, PhD
Joost Kummeling, MD-PhD student
Britt Mossink, Msc PhD student
Moritz Negwer, Msc PhD student
Prof. Jos Egger, clinical neuropsychologist

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Our work on the *EHMT1* gene and Kleefstra syndrome started from 2002 onwards, when we identified through a chromosomal translocation breakpoint study the disruption of the *EHMT1* gene as the most likely cause for the intellectual disability (ID) in a patient with features of a so far unknown syndrome. Through our clinical expertise we could identify phenotypically similar patients and subsequently definitely proof that so called heterozygous loss-of-function of the *EHMT1* gene is causative for this ID/autism spectrum disorder (ASD) condition, which is now commonly known as Kleefstra syndrome. After this discovery, we built a full translational pipeline and have taken major efforts to understand the genetic cause and unravel the pathogenesis of this syndrome to find ways to improve therapeutic interventions for the affected patients. In our group we focus on the developmental and neuropsychiatric phenotypes and observed significant psychopathology in patients with *EHMT1* mutations that we now further tackle in coordinating an international longitudinal study where we have involved the Boston and Manchester teams, and probably John Hopkins added when protocol and contracts are finalised (funded through Dutch national health care organisation: ZonMW).

In parallel, we extensively study cellular and animal models (fruitfly and mouse).
Moreover, we have collected fibroblasts from several of our patients and established human induced pluripotent stem cells (hiPSCs) that we differentiated into excitatory cortical neurons and other neural lineages. Relevant for our clinical observations, these findings provide an excellent *in vitro* platform to test the effects and efficacy of potential drugs on either animal models and various hiPSC-derived neural cell types.

**Thesis studies fully dedicated to KS and EHMT1:**
**Completed**
Monique Balemans
Phenotyping the *Ehmt-/-* Mouse as a model for Kleefstra syndrome (2013)
Tom Koemans
Converging molecular networks affected in Kleefstra syndrome and related neurodevelopmental disorders (2018)

Marco Benevento
The epigenetic role of the Kleefstra syndrome protein EHMT1 in synaptic scaling and cognition. (2017)

Karlijn Vermeulen
Endophynotyping: on the intersection of Psychiatry and Genetics (2018)

Ongoing:
Britt Mossink
Joost Kummeling: Tackling defective epigenetic assembly in psychopathology: Towards personalized intervention in rare genetic syndromes

Major funding by our team

Radboud university medical center/Donders Institute for Brain, Behaviour and Cognition. Various PhD projects.


European Union: IMPACT: Identification of converging Molecular Pathways Across Chromatinopathies as Targets for Therapy. ERARE18-144.

Dutch HCO ZonMW: Tackling defective epigenetic assembly in psychopathology: Towards personalized intervention in Kleefstra syndrome

References by our team on KS/EHMT1


