

## **GENETIC AND EPIGENETIC NETWORKS DISRUPTED IN INTELLECTUAL DISABILITY**

VAN BOKHOVEN H.

Department of Human Genetics, Molecular Neurogenetics Unit, Radboud University Nijmegen Medical Centre, Box 9101, 6500 HB Nijmegen (The Netherlands)

*Intellectual disability, genes, epigenetic, network, chromatin*

Intellectual disabilities (ID) comprise a highly diverse group of cognitive disorders. Gene defects account for about half of all patients and mutations causative for impaired cognition have been identified in more than 400 genes. While there are numerous genetic defects underlying ID, a more limited number of pathways is emerging whose disruption appears to be shared by groups of ID genes, for example . One of these common pathways is composed of ID genes that encode regulators of chromatin structure and of chromatin-mediated transcription regulation. Already more than 20 “epigenetic ID genes” have been identified and this number is likely to increase in the coming years when deep sequencing of exomes and genomes will become commonplace. Prominent examples of epigenetic ID proteins include the methyl CpG-binding protein MECP2, involved in Rett syndrome, the CREB binding protein CBP (Rubinstein-Taybi syndrome) and euchromatin histone methyltransferase 1 (EHMT1; Kleeftstra syndrome). Interestingly, several epigenetic ID proteins have been found to directly interact with one another or act together in complexes that regulate the local chromatin structure at target genes. Thus, it appears that the functions of individual epigenetic ID proteins converge onto similar biological processes that are crucial to neuronal processes. The next challenge will be to gain more insight into patterns of altered DNA methylation and histone modifications that are caused by epigenetic gene mutations and how these will disrupt the brain-specific expression of target genes. To that end, we follow a multi-level strategy that besides neurogenetics includes functional genomics which encompasses the generation and characterization of model organisms (mouse, rat and *Drosophila*) and molecular & cellular neurobiology to dissect molecular and cellular mechanisms that are key to learning and memory. Such research may reveal that a wide variety of mutations in the genetic code result in a more limited number of disruptions to the epigenetic code. If so, this will provide a rationale for therapeutic strategies.