CENTRE FOR INTEGRATIVE SEQUENCING

The BRD1 gene and interactome in psychiatric disorders

The bromodomain containing 1 gene (BRD1) has repeatedly been shown to be associated with schizophrenia (SZ) and bipolar disorder (BD) - initially by studies in extended families and more recently in large case-control samples and family-based replication studies. BRD1 encodes the BRD1 protein for which data suggest a role in transcriptional regulation through its participation in chromatin remodeling complexes.

Our overall aim is to characterize the involvement of BRD1 in the pathogenesis of SZ and BD. To do so, we have performed a range of genomics and proteomics investigations in genetically modified cell lines and mice as well as in DNA samples from large cohorts of patients. By this mean, we have discovered several novel protein interactions of BRD1 including interactions with proteins encoded by other SZ and BD risk genes (PBRM1 and YWHAE). We have also found that BRD1 primarily binds to promoter regions within the genome of cell lines stably expressing different isoforms of the protein and that the genes located immediately downstream of these binding sites are enriched with genes showing a high degree of genetic association to SZ and BD in human samples. Mice heterozygous for a constitutively inactivated allele of the *BRD1* gene show gender specific abnormal behaviors across a spectrum of schizophrenia and depression equivalent phenotypes combined with alterations in striatal dopamine, cortical GABA-mediated synaptic transmission and neuronal morphology indicating a key role of BRD1 in the normal functioning of the central nervous system and in the etiology of SZ and BD. In order to more specifically point towards the molecular causes of these phenotypes, we have performed RNAseq-based comparative transcriptome analysis of RNA extracted from amygdala and hippocampus CA3 micropunches from the mice. The genes being differentially expressed in these studies were significantly enriched with neuroactive ligand-receptor interaction and calcium signalling pathway genes as well as cell-cell signalling, transmission of nerve impulse, ion transport and neuron development associated genes.

Thus, BRD1 seems to be an important regulator of gene expression in the brain and a key factor governing normal behavior, cognition and neurotransmission.

Presentations:

Anders Børglum

Identification of *BRD1* as a risk gene in schizophrenia and bipolar disorder

Jane H. Christensen

Investigating the BRD1 interactome and the importance of BRD1 in the central nervous system

Anto Rajkumar

Investigating neuronal morphology and transcriptome of female $BRD1^{+/-}$ mice