Attention deficit hyperactivity disorder (ADHD) is one of the most common and most heritable childhood onset psychiatric conditions. Children with ADHD are at high risk of developing antisocial behavior, substance abuse and other psychiatric disorders, consequently presenting difficulties in their education and social integration.

Despite being one the most heritable psychiatric disorders, the genetic background of ADHD is still unknown. The main aim of this project (EPIMEN) was to establish a network to investigate epigenetics of ADHD in the form of parent of origin effects (POE). The design of this project involved two steps: (1) performance of genome-wide scan to identify candidate genetic loci revealing parent of origin effects in ADHD and (2) examination of methylation patterns of such loci in ADHD. In addition, being an integration grant, a crucial element of this project was also to integrate into scientific community of ADHD genetics by establishing working collaborations with leading groups in the field.

To achieve the first goal, we proposed to use log-linear modeling (never used in ADHD genetics before) in a large sample of trios (~10,000) in order to obtain the needed power. The sample was planned to consist of ~2,000 trios collected through Psychiatric Genomics Consortium (PGC) and ~9,000 trios the Norwegian Mother Child (MoBa) cohort. The PGC dataset consists of trios with affected child. MoBa trios, on the other hand, were selected randomly from the general Norwegian population and, thus, do not have ADHD diagnosis. Instead, a score reflecting ADHD DSM-IV symptoms was planned to be used as ADHD phenotype in MoBa trios.

During this project, we have established a working collaboration with PGC at BROAD Institute (Boston, MA, USA) and were granted access to the trio sample in this consortium (2,050 trios in total) for our analyses. We have performed log-linear modeling in each of PGC trio datasets (4 samples in total), followed by inverse variance meta-analysis of the obtained summary statistics. Figure 1 reflects quantile-quantile plots of the meta-results, showing that there is no obvious technical issue with the analyses. Overall, we did not observe any genome-wide significant hit, most probably, due to the lack of power. In the subsequent steps of this project, we were planning on examining the candidate regions identified at this stage in a larger MoBa trio sample.

We have established a scientific dialog with MoBa, the genetic data of which was scheduled to be released by January 2016. However, due to delay in MoBa, no data was made available. After further individual negotiations with MoBa, we are expected to receive data in November 2016. Given the delay in MoBa data release, we were unable to evaluate our preliminary candidate parent-of-origin regions identified in PGC trios as well as perform the overall meta-analysis. However, as we are expected to receive the MoBa data in November 2016, exciting results are expected soon.

In the meantime, we turned out focus to the development of new methodology to examine POE in continuous traits. So far, the log-linear modeling of POE, which allows us to evaluate various aspects and confounders in POE (association, maternal effect and imprinting), is only available for dichotomous traits. Thus, there is the need for new methodology that can be applied to POE analyses in continuous traits. To pursue this aspiration, we obtained additional funding for me to spend 6 months at BROAD Institute (Boston, MA, USA) in the group of Benjamin Neale where I have been working on developing the new method for the past 4 months (since July 2016). We have successfully established a POE model with parameterization suitable for POE detection in continuous traits. Given the delay of MoBa data, we have evaluated the new model in simulations. Figure 2 reflects the various effects and confounders of parent-of-origin analyses that were detected by our method under various values of heritability. We will apply the developed method to

the MoBa trio data as soon as it becomes available.

The second goal of this proposal was to investigate methylation patterns of significant loci identified in statistical analyses of trio data as well as to evaluate the differences in methylation patterns between ADHD cases and controls. As the meta-analyses are delayed due to MoBa release, it was difficult to know which loci should be examined. Thus, we focused on obtaining genome-wide methylation data for ADHD cases and controls that will also allow us to achieve our goals at a later time point. We have collected and successfully genotyped 128 individuals (70 adult ADHD cases and 58 controls) on Illumina 850K EPIC methylation array. This array is the latest, state-of-the-art array that allows us to obtain the widest coverage of methylation sites that an array technology allows to date. We have also established a collaboration with Prof Barbara Franke (Radboud University, Nijmegen, the Netherlands), who shares our interest in methylation patters in adult ADHD. Together with Prof Franke, we will be able to increase our sample size (additional 70 subjects genotyped on EPIC assay) and tackle the questions of methylation in adult ADHD.

Figure 1. Summary of parent-of-origin meta-analysis performed in PGC ADHD trios.

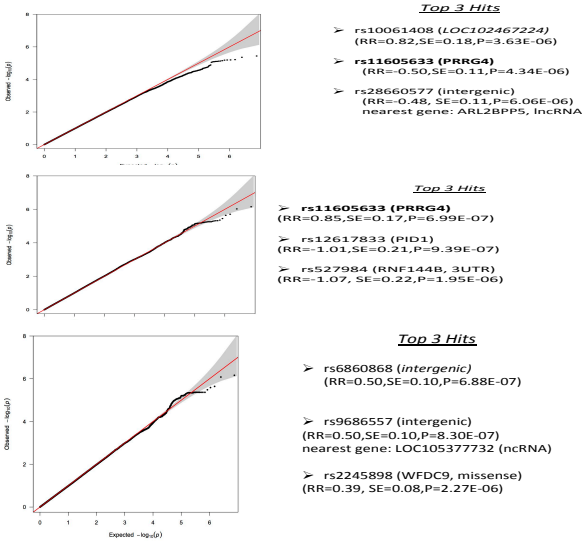

Figure 2. Results of simulations to detect parent-of-origin effects with newly developed model for continuous traits.