Programme

# iPSYCH Annual Meeting 2019 - Tuesday 21 to Thursday 23 May

## Day 1

07:30 - 10:30 **Bus from Aarhus: BSS Aarhus University, Fuglesangs Allé 4, 8210 Aarhus V**

Departure at 07.30. Look for the bus with an iPSYCH logo.

09:00 - 10:30 **Bus from Copenhagen/Valby St., Lyhøjgaardsvej, 2500 Valby**

Departure at 09.00. Look for the bus with an iPSYCH logo.

10:30 - 11:00 **Arrival at Comwell Klarskovgaard**

11:00 - 11:15 

**Welcome and opening remarks by Preben Bo Mortensen**

11:15 - 12:05 

**PsycheMERGE: Advancing precision psychiatry through EHR-based genomics by Lea Davis**

Lea Davis is an Assistant Professor of Genetic Medicine, Psychiatry and Behavioral Sciences, and Biomedical Informatics. Dr. Davis' work employs a population level approach to the investigation of the genetic basis of a wide range of complex phenotypes.

Her research aims to discover how polygenic risk, rare variant risk, and environment interact to result in common psychiatric diagnoses and their comorbidities. To accomplish this goal, she applies genomic and bioinformatic approaches to biobank data and phenotypes extracted from the electronic health record. In addition to her work on psychiatric genomics, Dr. Davis has a long-standing interest in research ethics, genomic privacy, and data sharing.

12:05 - 13:00 **Lunch**

13:00 - 13:50 

**Epigenome-wide association studies of aggressive behaviour and by Jenny van Dongen**

Jenny van Dongen is an assistant professor at the department of Biological Psychology at the VU Amsterdam. She works with data from the Netherlands Twin Register to study the causes of individual differences in DNA methylation and the connections between epigenetic mechanisms and behavior and health.

Dr. van Dongen has a Bachelor's degree in Biology and Master's degree in Neuroscience, and obtained her PhD at the VU Amsterdam in 2015.

Since she obtained her PhD, she has worked on a national collaborative project (the BIOS consortium) and on an international project (ACTION). Within the BIOS consortium (http://www.bbmri.nl/acquisition-use-analyze/bios/), she works together with multiple Dutch biobanks to study the interplay between genome, epigenome, transcriptome, and complex traits, and led an epigenome-wide association study meta-analysis of educational attainment.

She also established a catalogue of individual differences in DNA methylation that contains information on the total heritability and SNP heritability of DNA methylation level at genome-wide sites in blood, and information on sex and age differences in genetic and environmental variance (http://bbmri.researchlumc.nl/atlas/).

Within ACTION (http://www.action-euproject.eu/), she has performed an epigenome-wide association study meta-analysis of ADHD symptoms in adults and currently leads an epigenome-wide association study meta-analysis of aggressive behavior for which she collaborates with 20 cohorts from around the world.

13:50 - 14:30

### New iPSYCH genotyping data (iPSYCH2015): update on QC, imputation, and PRS

Comfy chair: Jakob Grove
Presenters: Esben Agerbo, Andrew Schork, and Bjarni Vilhjálmsson

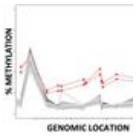
iPSYCH2015/6 means a welcome increase of sample size, but comes with an increase of the complexity as well with a number of different genotyping chips employed in the different subsamples. This poses a number of challenges to imputation and downstream analyses. In part one of this session, we will illustrate what some of these challenges are, what potential solutions we see and how to compare them. Moreover, we will provide the status of the current efforts being made in iPSYCH on these matters, and the projected timeline.

In the second part, we give an overview of current PRS generation activities in iPSYCH, explain what is currently available in terms of different PRS, and what plans there are for future PRS generation.

14:30 - 15:00

### Coffee/tea break

15:00 - 16:15




### Symposium I - Epigenetic contributions to mental disorders

Chair: Anna Starnawska - Moderator: Nicklas Heine Staunstrup

Presentations:
a) Neonatal epigenome-wide association studies of ADHD, ASD and their PRS by Anna Starnawska

b) Sex-specific epigenetic profiles and their link to mental disorders by Nicklas Heine Staunstrup

c) Rare epimutations in ASD by Magdalena Janecka

d) Parent of origin effect in ASD by Christine Søholm Hansen

Abstract:
The epigenome is believed to be a key 'missing piece' of the aetiological puzzle for complex phenotypes. It plays a pivotal role in regulation of human brain development, its functioning, and aberrant changes in this modification are increasingly reported to be associated with mental disorders.

In this symposium we will present results from four different analytical approaches to investigate epigenetic contributions to mental disorders, with special focus on ADHD and ASD. We will present results from neonatal epigenome-wide association studies of ADHD, ASD, comorbid ADHD and ASD, as well as results from associations between their polygenic risk scores and neonatal epigenetic landscape. Then we will answer a question if rare epimutations in the neonatal epigenome are linked with increased risk of ASD and if they are associated with rare exome sequence variation in the genome. Next we will present our journey to identify genome-wide significant association with paternal over transmission in ASD, but not associated with ADHD, of variants in the genomic region of the DDC gene, and our exploration of epigenetic mechanisms contributing to this parent of origin effect. Last but not least, we will uncover how neonatal epigenetic differences between males and females are related to brain development, development of mental disorders and sex-bias observed across psychiatric phenotypes.

16:15 - 17:15

### Business meeting: Schizophrenia GWAS (Location: Room K2)

Participants: Michael E Benros, Xueping Liu, Andrew Schork, Alfonso Buil Demur, Preben Bo Mortensen, Thomas Werge, Merete Nordentoft, Thomas Als and Anders Børglum

17:30 - 18:30

### PIF 'meeting' (Location: Udsigten)

Participants: Merete Nordentoft, Anders Børglum, Preben Bo Mortensen, Thomas Werge, Ole Mors, David Hougaard and Kristjar Skajaa

18:30 - 20:00

### Dinner

20:00 - 22:00 **Poster Session**

ADHD genetic liability and drug treatment outcomes
Isabell Brikell

Choice of imputation strategy and effect on complex trait analyses
Vivek Appadurai

Contribution of common genetic risk variants to intellectual disability: a genome-wide association study from a large Danish population-based cohort
Rebeca Garcia Gonzale

Diagnostic and genetic heterogeneity in ADHD: iPSYCH1.5 GWAS
Sonja Labianca

Effects of globin mRNA depletion on the whole blood transcriptome
Victor Yakimov

EWAS of pregnancy and birth complications
Anna Starnawska

Examining sex differences in shared aetiology across neuropsychiatric and behavioural traits
Joanna Martin

Exposure to air pollution in early childhood and the association with ADHD
Malene Thygesen

Generation of the World's first genetic large animal model of schizophrenia and bipolar disorder
Per Qvist

Genetic association study of psychotic experiences in UK Biobank
Sophie Legge

Genetic Liability to ADHD and Substance Use Disorders in Individuals with ADHD
Theresa Wimberley Böttger

Genomic predictors of the risk of transitioning from first episode depression to severe mental disorders
Morten Krebs

Genotype-phenotype relationships in children with Copy Number Variants associated with high neuropsychiatric risk
Samuel Chawner

Investigating the association of maternal severe mental illness and exposure to obstetric complications with rates of intellectual disability in children
Patsy Di Prinzio

Is congenital blindness protective for schizophrenia and other psychotic illness?
Vera Morgan

Network enrichment analysis in schizophrenia bridging genetics and -omics
Camellia Sarkar

Neurocognitive Heterogeneity in 7-Year-Old Children at Familial High Risk of Schizophrenia or Bipolar Disorder
Nicoline Hemager

Neuropsin regulation in health and disease
Lina Bukowski

Paternal origin Dopa Decarboxylase (DDC) gene variants are associated with Autism Spectrum Disorder
Christine Søholm Hansen

Polygenic risk, parental history and conversion from depression to bipolar disorder
Katherine Musliner

Psychopathological trajectories from age 7 to age 9 in a cohort of children with familial high risk of schizophrenia and bipolar disorder
Ditte Ellersgaard

Sex chromosome Aneuploidies in iPSYCH population case cohort
Xabier Calle

The impact of population structure on summary-based polygenic inference
Bjarni Vilhjalmsson

Validation of a genetic mouse model of autism spectrum disorder
Maja Fuhlendorff Jensen

## Day 2

07:00 - 08:30 **Breakfast**

08:30 - 09:20

### Transdiagnostic Genomics for Precision Medicine in Psychiatry by Stephan Ripke

Stephan is a key analyst of the Psychiatric Genomics Consortium (PGC), a collaborative effort that involves hundreds datasets from research groups from more than 30 countries. To do this, he has created a computer pipeline that standardizes data, imputes missing values, performs the final analysis and brings the results into displayable format (e.g. the Web based toolRICOPILI). This collection of computer programs is unique in its ability to analyze millions and millions of data points in a short period of time, a critical ability that has allowed genome-wide association studies of psychiatric data to produce concrete results.

Stephan's current GWAS research focuses on schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder, attention deficit hyperactivity disorder, and cross-disease analyses.

09:20 - 09:50

### Coffee/tea break

09:50 - 10:40

### Large-scale studies to identify causal genes for psychiatric traits by Bogdan Pasaniuc

Bogdan Pasaniuc is an associate professor of Computational Medicine, Human Genetics and Pathology&Lab Medicine at UCLA.

His group develops statistical and computational methods to understand the genetic basis of disease, focusing on under-represented populations, integrative genomics, and biobank studies. His group developed new methodologies to integrate epigenetic profiles within trans-ethnic studies to localize causal variants in post-GWAS studies. More recently, his group introduced transcriptome-wide studies based on gene expression imputation as a principled approach to localize causal genes for complex traits, and applied such approaches to identify new risk genes for multiple complex traits such as Schizophrenia.

10:40 - 11:30

### Symposium II - Update on results from GWASs of secondary phenotypes

Chair: Ditte Demontis - Moderator: Thomas D. Als

Presentations:
a) Identification of the first genome-wide significant risk loci for nocturnal enuresis (bed wetting) by Jane Hvarregaard Christensen

b) GWAS of disruptive behavior disorders in the context of ADHD identifies a genome-wide significant risk locus and large genetic overlap with aggressive and and anti-social behaviours by Ditte Demontis

c) The role of common genetic variants in response to antidepressant treatment by Thomas D. Als

d) Genome-wide association study of Danish and math school grades reveals novel insights into genetic architecture of educational attainment by Veera Manikandan

Abstract:
The large number of genotyped individuals in the iPSYCH cohort makes it a valuable source for doing large genetic studies of other phenotypes than the primary disorders studied in iPSYCH. In this symposium preliminary results from genome-wide association studies of four secondary phenotypes will be presented.

First a presentation of results from a GWAS of nocturnal enuresis based on information of diagnoses and desmopressin prescriptions. The analysis included 3,884 cases and 31,073 controls and identified six variants surpassing genome-wide significance in two independent loci. The study provides important new information about the biology underlying a disorder affecting up to 15% of all 7-year-old children.

Second a presentation of a GWAS meta-analysis of ADHD comorbid with disruptive behavior disorders (DBDs; which include conduct disorders and oppositional defiant disorder). The GWAS was based in individuals from the iPSYCH cohort and eight cohorts from the Psychaitric Genomics Consortium in total 4,471 cases and 32,857 controls. The study identified one, well supported genome-wide significant risk locus and strong enrichment in variants associated with aggressive and anti-social behavior in individuals having ADHD comorbid with DBDs compared to controls and also to a larger extent than individuals having ADHD without DBDs.

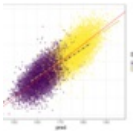
Third a presentation of a study aiming at characterizing the common genetic architecture of response to antidepressant treatment. Antidepressent treatment has previously been shown to be heritable in cases with Major Depression, however is this also the case in the iPSYCH cohort, when extracting information regarding treatment response from the Danish National Prescription and Hospital Registers? SNP-heritability estimates using approaches implemented in GCTA-GREML will be presented.

Fourth a presentation of the to-date largest GWAS of educational attainment based on Danish and math school grades in 32,125 individuals from iPSYCH. The study demonstrates an almost complete overlap of genetic variants that affect the number of school years with the variants that affects the Danish and math skills captured by school grades. However, GWAS analyses of Danish-specific and math-specific achievements showed that the genetic correlations of Danish-specific achievement with various phenotypes were significantly different from the genetic correlations of math-specific achievement, hence revealing a previously-unknown significant heterogeneity in the genetic architecture of EA.

11:30 - 12:30

### Lunch

12:30 - 13:30



### Symposium III - Dissecting the polygenic score

Chair and moderator: Bjarni Vilhjálmsson

Presentations:
a) Limits of polygenic risk prediction: heritability estimation across disease architectures by Bogdan Pasaniuc

b) Improving polygenic risk scores by incorporating estimates of heritability enrichments by Doug Speed

c) Subtype analyses using PRS by Jakob Grove

d) A Geneticist's Illusion? Implications for PRS? by Andrew Schork

Abstract:
Polygenic risk scores (PRS) have in recent years become a cornerstone for studying the etiology of common and complex diseases. By aggregating thousands of genetic contributions, polygenic risk scores often dwarf contributions from other known individual risk factors for the disease or trait in question. Polygenic scores have thus proven useful for studying the genetic architecture of diseases as well as a promising tool for identifying at-risk individuals in clinical applications.

In epidemiology, and social sciences, polygenic scores can increase statistical power to detect environmental risk factors as well as provide insight into the relationship between environmental and genetic effects. As sample sizes in genome-wide association studies (GWAS) continue to increasea, and more phenotypes are studied, the value of polygenic scores is expected to increase. The aim of this symposium is to provide an overview of polygenic scores and their potential for studying psychiatric disorders.

The four presentations will discuss limitations of polygenic scores, how to improve polygenic scores, and other applications of polygenic scores.

13:30 - 14:00

### Coffee/tea break

14:00 - 14:30

### iPSYCH exome sequencing and its contribution to Autism Sequencing Consortium gene discovery by Kyle Satterstrom

F. Kyle Satterstrom is a Computational Biologist at the Broad Institute of MIT & Harvard and the Analytic & Translational Genetics Unit of Massachusetts General Hospital.

He works in the laboratory of Mark Daly, where he focuses on analyzing large exome sequence datasets to identify genetic risk factors associated with psychiatric disorders such as autism and ADHD. Recently, he has helped lead analyses of the exomes generated by iPSYCH, both separately as well as jointly with those collected by the Autism Sequencing Consortium.

Kyle conducted his PhD dissertation research in a Cell Biology laboratory at Harvard Medical School, combining experimental and computational methods to study enzymes involved in metabolism and aging. He received his bachelor's degree in Chemistry & Physics from Harvard in 2004, writing a senior thesis about alchemy in New England in the seventeenth century.

14:30 - 15:00

### The influence of intellectual disability on gene discovery in severe childhood developmental disorders by Jack A. Kosmicki

Jack A. Kosmicki is a PhD student at Harvard Medical School in the bioinformatics and integrative genomics PhD program.

He is doing his dissertation in Mark Daly's laboratory at Massachusetts General Hospital and the Broad Institute where he focuses on analyzing large family-based exome sequencing datasets to identify de novo and inherited genetic risk factors associated with neurodevelopmental disorders such as autism and intellectual disability / developmental delay. Recently, he spearheaded analyses of the exomes generated by the Autism Sequencing Consortium to identify 102 genes conferring risk for ASD.

He previously graduated summa cum laude from the University of Northern Iowa in 2008 with two bachelor degrees in bioinformatics and biology.

15:00 - 16:00

### Business meeting: GxE in Depression (Location: Room K1)

Participants: Katherine Musliner, Nis Suppli, Esben Agerbo, Veera M Rajagopal, Viviek Appadurai(?), Thomas Als, Jakob Grove, David Hougaard, Michael Benros, Trine Munk-Olsen, Andrew Schork, Thomas Werge, Ole Mors(?), Anders Børglum, Merete Nordentoft and Preben Bo Mortensen

16:00 - 17:00

### Business meeting: Analytic strategy for VIA7/VIA11 data (Location: Room K2)

Participants: Merete Nordentoft, Ole Mors, Vibeke Bliksted, Aja N Greve, Ditte Ellersgaard, Nicoline Hemager, Jamal Uddin, Claus Ekstrøm and Anders Helles Carlsen

17:00 - 18:00

### Business meeting: Genetic predictors of suicidal behavior (Location: Room K1)

Participants: Annette Erlangsen, Merete Nordentoft, Esben Agerbo, Ole Mors, Wes Thompson, Anna Starnawska, Ditte Demontis and Anders Børglum

18:00 - 20:30

### Gala dinner

20:30 - 21:30

### Social event

## Day 3

07:00 - 08:30 **Breakfast**

08:30 - 09:20

### Metabolomics and lipidomics as an approach to study Alzheimer's disease by Cristina Legido Quigley

Cristina Legido-Quigley's is a Principal Investigator in Systems Medicine Department, Steno Diabetes Centre, Copenhagen, and an Associate Professor in Chemistry and Chemical Biology – IPS, School of Medicine and Biomedical Sciences, King's College London, UK.

Her work is at the interface between chemistry and medicine and she is an expert in metabolomics and lipidomics as analytical methodologies. This is a data-rich science that allows for the detection of thousands of small molecules and lipids in order to understand the underlying biology in disease.

Another aspect to her work is to integrate multi-omics and clinical data to design diagnostic tools to stratify patients into treatments. She is specially interested in metabolic crosstalk between the liver and brain and specifically in links between metabolic syndrome and neurodegeneration/cognition problems.

09:20 - 10:10

### EnGagE - Pan-European Network Enhancing Psychiatric Genetic Counselling, Testing and Training in Europe by Franziska Degenhardt

Franziska Degenhardt is a board certified clinical geneticist at the Institute of Human Genetics, University of Bonn, Germany. Since 2015, she has been head of a research group focusing on the identification of genetic risk factors for psychosis. In 2017, she qualified as a senior lecturer in clinical genetics (Habilitation).

In the clinical context, she provides genetic counselling to patients, families, and individuals at risk of genetic-related disorders with particular focus on patients with a psychiatric disorder. In January 2018, she was appointed co-chair of the Genetic Testing Committee of the International Society of Psychiatric Genetics (ISPG).

In April 2018, Franziska Degenhardt secured funding from the European Union for the establishment of a pan-European network to Enhance Psychiatric Genetic Counselling, Testing, and Training in Europe (EnGagE). For the first time, a critical mass of expertise from across Europe and beyond is assembled to develop a joint research and clinical agenda for the implementation of the emerging disciplines of Psychiatric Genetic Counselling and Psychiatric Genetic Testing in (future) routine psychiatric clinical practice and professional training within Europe.

10:10 - 10:40 **Coffee/tea break**

10:40 - 11:30

### Children born with familial high risk for schizophrenia or bipolar disorder – What have we learnt from The Danish High Risk and Resilience Study – VIA 7? by Aja Neergaard Greve and Nicoline Hemager

ABSTRACT

Introduction

Children born to parents with schizophrenia or bipolar disorder have been studied for decades and it is well-known that they have a higher risk for developing mental illness as well as a wide range of social, cognitive and motor impairments. However, most studies have included children with wide age ranges and have recruited offspring from patients in current treatment. Our aim was to investigate a representative cohort of 7-year-old children at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) and to compare them with a control group. Further, we aimed at characterizing cross-diagnostic heterogeneity.

Methods

We recruited 522 7-year-old children from all over Denmark through the Danish registers. Participants included 202 children with FHR-SZ, 120 children with FHR-BP and 200 population-based control children. The assessors were blinded to risk status. We used a comprehensive test battery to assess the children in several domains including psychopathology, motor and language development, social cognition, neurocognition and the home environment. A multi informant approach ensured information from both parents and teachers. Hierarchical cluster analysis (HCA) was used to identify cross-domain subgroups.

Results

Children with a familial predisposition for schizophrenia demonstrated widespread impairments across the domains of neurocognition, social cognition, language, motor functions as well as a higher prevalence of lifetime psychiatric diagnoses and insufficient home environment compared with controls. Children with a familial predisposition for bipolar disorder demonstrated either less pronounced deficits or intact functions. Four distinct cross-domain subgroups were identified and revealed particularly vulnerable versus more intact subgroups. Clusters were significantly associated with level of functioning, adequacy of the home environment, and the polygenic risk score for educational attainment.

Conclusion

Children with FHR-SZ and, to a lesser extent, children with FHR-BP present with widespread impairments already at age 7. Cross-diagnostic heterogeneity suggests that there are subgroups with more pronounced impairments across domains which calls for the development of early intervention strategies to ameliorate deficits and reduce the risk of transition to mental illness.

11:30 - 11:45 **Closing remarks**

12:00 - 12:15 **Sandwich to go and departure**

12:15 - 13:30 **Bus to Copenhagen/Valby St., Lyshøjgaardsvej, 2500 Valby**

Expected arrival at 13.30.

12:15 - 15:00 **Bus to Aarhus, Fuglesangs Alle 4, 8210 Aarhus V**

Expected arrival at 15.00.