Title Slide

Slide 1

Welcome to my Midway Evaluation. I hope to convey to you my interest in my PhD project which has held my attention these last two years. And for which I am still greatly enthused despite the different challenges that the corona pandemic has given. I am working under the supervision of Stephanie Le Hellard and Anne-Kristin Stavrum here in Bergen. I am also co-supervised by Tetyana Zayats at the Broad Institute and Ingrid Melle at NORMENT/UiO.

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The focus of my project is to identify epigenetic marks on the DNA that result from environmental contact or impact – within the context of psychiatric disorders such as schizophrenia, bipolar disorder and major depressive disorder.

Methods –

Aims -

Status of projects -

History of definition of epigenetics

Slide 3

Show complex picture of epigenetic landscape

We will be focusing on DNA methylation at cytosine positions – these are positions where a methyl group is covalently bound to a cytosine located immediately adjacent to a guanine. DNA methylation is one area of epigenetics that has been actively studied for several reasons:

Perhaps in a nutshell I could say that it is because DNAm tells us so much from the perspective of development, development, development.

* Plays an essential role in development and tissue differentiation (Reik)
* Key role in determining transcription factor binding and enhancer function during development (Ziller)
* DNAm is highly tissue and cell-type specific
* DNAm is highly malleable, and has been shown to be influenced by many environmental exposures, including diet, levels of *in utero*  nutrients and smoking (15-19)
* DNAm landscape changes dramatically as a function of age (20), cancer (20) and complex diseases (3)
* Thus, DNAm represents not only an attractive disease biomarker, but also offers to improve our understanding of the interface between environmental risk factors and disease phenotypes (3, 17 21).
* For these reasons DNA methylation provides important information in the study of severe psychiatric disorders that are neurodevelopmental, such as SCZ, and how the medications used to treat these disorders manifest either therapeutic or adverse effects.

Different functions – Jordana Bells’s paper

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Examples of environmental influences: from healthy habits such diet and exercise, to harmful habits such smoking and alcohol abuse. In our group we are currently evaluating the impact of cannabis in psychosis, as well as a history of childhood trauma in these disorders.

epigenetic research suggests molecular connections between the environment, genetics, and how acquired characteristics may be inherited across generations.

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The topic of epigenetic inheritance is of interest to us as we seek to understand the mechanisms that either set the stage for vulnerability in the next generation, or even increase the risk of adverse physical or mental health.

The experience of trauma, in particular historical trauma, is of interest when looking at severe mental illness and the epigenetic markers associated with trauma. The transgenerational effects on health outcomes have been reported on from the Dutch Hunger Winter, the seasons of famine from Sweden and the histories of Jewish children raised in USA compared to Europe following WWII. Currently, the effects of transgenerational historical trauma are being studied in individuals whose parents or grandparents were removed from their families and interned in boarding schools for Native Americans in the US and Canada.

What did they find for the Dutch Hunger Winter – metabolic, cardiovascular and increased risk of schizophrenia.

What did they find for the Swedish famine winters? Pennbrook?

What have they found for First Nation people?

1. One of the ways in which epigenetic changes have been shown to manifest is in the way one responds to stress or trauma experienced in their lives.189
2. 189. Bombay, et al, “The Intergenerational Effects of Indian Residential Schools,” 320–338; K. L. Walters, K. S. A. Mohammed, T. Evans-Campbell, R. E. Beltrán, D. H. Chae, and B. Duran,
3. 50
4. “Bodies Don’t Just Tell Stories; They Tell Histories: Embodiment of Historical Trauma among American Indians and Alaska Natives,” Du Bois Review: Social Science Research on Race 8:1(2011), 179–189.
5. “Intergenerational transfer of psychological distress.
6. Ehlers et al. (2012) proposed that PTSD symptoms in AI/AN populations were heritable, meaning that having a parent with PTSD symptoms may increase the next generation’s lifetime experience of PTSD symptoms.194 While this study of two-spirit boarding school attendees  
   is not specific about the time period of school attendance, generalized anxiety disorder and incidence of PTSD symptoms (but not a formal PTSD diagnosis) were higher among those who had a caretaker who attended boarding school. The heritability of PTSD has been found in other studies among Holocaust survivors and their children.195
7. Descendants of boarding school alumni appeared to have more exposure to stressors and to also be more affected by stressors. Sensitivity to stressors may come from HPA axis activation or dysregulation  
   or neurochemical function in limbic and frontal cortical regions.201 Children of residential school alumni responded more poorly to stressors than controls, leading investigators to conclude that adverse childhood experiences may limit the ability to function successfully in adulthood, thereby increasing the likelihood of experiencing stressful situations.202

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Definition of psychosis

Something twin study

DNA methylation findings for SZ

Slide 7

DNAm findings in pharma.

We don´t know how the drugs work – except for the dopamine hypothesis

Why is it important to study this?

Metabolic side effects of the medications, impact to health following chronic administration for years.

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Challenges to this work: We are evaluating DNAm extracted from cells sampled from peripheral blood. We have two issues: 1) what can the blood tell us about a disorder that is brain-based?, 2) blood cell proportions change according to diet, health status, time of day.

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We decided to look at time of day – and circadian rhythms.

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Paper about circadian pharma – Corneliessen

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