Slide 2 ##Epigenetics - Smigielski

This is a complex picture of the epigenetic landscape that portrays cellular activities from histone modifications, microRNAs and DNA methylation. There is crosstalk between the different mechanisms, and DNAm, posttranslational histone modifications and non-coding RNA all have an important role in the etiology of major psychosis (Gerscher et al., 2018). DNA methylation however is the most widely studied epigenetic mechanism and is the subject of this talk. And specifically, I will be talking about DNA methylation at cytosines that sit adjacent to guanines. I’ll refer to these as CpGs, or DNAm marks.

Slide 3 ##Background - Psychosis

Symptoms in SCZ, BPD and MDD – including non specificed

Identification of new biomarkers for these disorders is difficult, primarily because of the lack of knowledge about disease pathophysiology and mechanisms of drug action.

Slide 4 ## Background AP drugs

AP drugs – first line of treatment for psychosis

* Believed to work on neurotransmitter systems

- Efficient for hallucinations but less so for cognitive

The focus of SCZ research has been on the dysfunction thought to underlie changes in network activity across the brain – in particular, the balance between excitatory and inhibitory signaling. Glutamate (excitatory). GABA (inhibitory)

Neuropsychiatric drugs are grouped into various classes with slightly different mechanisms of action.

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##GWAS findings

Slide 5 ##EWAS findings for antipsychotics

1. Drug response-related DNAm remains poorly understood
2. Variety of methods, tissues assayed, study designs, sample sizes
3. Integration of genomic data and genome-wide DNAm data may be more effective – towards discovery of underlying drug response

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## Hypothesize

Common and specific

We hypothesize that differential DNA methylation associated with

AP drugs identified in the peripheral blood of individuals taking these drugs, independent of diagnosis

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## Factors that influence the efficacy of AP

Age: Significant impact on drug concentrationmost studies show increased concentration above age 60, but some, like Olanzapine and Quetiapine show changes every 5 to 10 years.

Sex: Women generally have dose-adjusted concentrations 20-30% higher than men (Castberg et all, 2017)

- Age, gender, smoking <br> <br />

- Genotype - i.e. metabolic enzymes <br> <br />

- Polypharmacy <br> <br />

- Time of day of administration <br> <br />

- Dose & Compliance - as monitored by serum values

Regulation of drug responses occurs at various levels including genetics, epigenetics, transcriptional, and protein modification, and also involves many functional pathways ([Amare et al., 2017](https://www.frontiersin.org/articles/10.3389/fnins.2021.674273/full" \l "B6))

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## TOP Cohort

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## Study/model design

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### Models selected for Quetiapine n=92

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### Results for CpGs at Genome-wide significance

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## Manhatten plots comparing the two models

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### Glycosylation

Regulates nearly all cellular processes

Glycans are necessary for proper protein folding, protein trafficking, cell-cell recognition, cell migration, etc. Gysosulation enzymes often function in a single pathway with only one or occasional a few enzymes capable of completing each step.

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### Disregulated glycosylation in SCZ

Presynaptic neuron in green, postsynapitic neuron in blue

In addition to genes involved in synaptic transmission and the immune system, several glycosulation enzymes are directly implicated in the pathogenesis of the disorder (Mealer, 2020)

Glycosulation may contribute to abnormal neuronal signaling and connectivity observed in SCZ. However, such changes may also results from exposures associated with the disease ((Williams, 2020)

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Glycosylation changes observed in SCZ span several brain regions, cellular pathways, classes of proteins, and steps of the synthetic pathway. This suggests a general dysregulation of glycosylation as a feature of the disease state and does not implicated a specific synthetic step or cell type as being uniquely vulnerable.

Articles in psychiatry. Williams and Mealer

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### GLT8D1 <br> - transcripts associated with SCZ and BPD

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Differentially Methylated Regions (DMRs) <br/>

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### Future prospects

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##Acknowledgements