Title Slide

Slide 2 Summer slide

I am going to present the final version of the project that is going in the manuscript – if the co-authors agree. Today the focus will be on the differentially methylated regions identified.

Slide 3 Aim: Identification of treatment effects

Olanzapine, quetiapine and risperidone – the drugs we are working with.

Our focus has always been on DNAm which has been shown to differ in individuals with severe mental illness compared to controls.

Characterization of epigenetic dysregulation is complex and identification of pathways – and the timing - where alterations may have occurred is not fully characterized.

Slide 4 Epigenetic modifications

While we study DNAm, we know that several epigenetic mechanisms work together. Other epigenetic factors, contribute to changes in the conformation of the chromatin.

Describe enzymes that demethylate or acetylate (readers and writers) That allow for differences in gene regulations

At present, it is difficult to determine which epigenetic regulations are essential for AP effects. It might require future studies using Chip-seq., RNA-seq., and genome-wide DNAm techniques-

So, what I decided to do in this final part of the project was to look at the DMRs that we identified and see if there was a relationship to any of the other genes associated with epigenetic factors.

Slide 5. Sample Selection

I simplified the analysis by selecting the sample samples for each analysis – although we included the medication – free in the specific effects group to help with power.

Slide 6 Methods

EpiFactors is a web-accessible database that provides curated information on human proteins and protein complexes involved in epigenetic regulatory mechanisms

Its focus is on cataloging the enzymes, complexes and other factors that catalyze or regulate different types of epigenetic modifications.

Slide 7 Results: Common Effects

Slide 8 Results: Specific Effects

Slide 9 Database investigation of DMR genes

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Slide 10 EpiFactors

Conclusion

Yes, we may have small sample sizes, and yet we have samples from individuals who have been on the medication for xxx. In the literature, larger meta-analyses show Median study duration 6 weeks, maximum 13 weeks (PMID:37159349)

Acknowledgements

So real-world observations studies are important to understand the long-term efficacy of AP. Usually these studies have longer follow-up periods compared to RCTs, and reflect a more accurate reflection of clinical practice. This is also a challenge as one study found that risperidone monotherapy had the highest txt discontinuation rate (TDR) and the shortest time to discontinuation (TTD), and olanzapine monotherapy was superior to polypharmacy in terms of long-term efficacy.

- Focus on response, rather than cross-sectional methylation status

- Real-world studies are also challenging - most are short term

- Treatment discontinuation rate (TDR) lower for monotherapy vs polypharmacy

- Risperidone highest TDR and shortest Time to discontinuation (TTD) (PMID: