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, rather, the developmental stage - where alterations important in psychosis development may have occurred is not fully known. (Waw

Slide 4 Epigenetic modifications

While we study DNAm, we know that several epigenetic mechanisms work together. Other epigenetic factors contribute to changes gene transcription or silencing, not to mention conformation of the chromatin. The most studied of these factors are enzymes that methylate, or acetylate histones, or remove these groups. Also of importance are the lncRNAs.

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

Nevertheless, 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 any association with epigenetic factors.

Slide 5. Sample Selection

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

Slide 6 Methods

Slide 7 Results: Common Effects

Slide 8 Results: Plotting KDM2B

No apparent association between serum values and methylation values. It could be that the relationship is non-linear and the correlation could be seen with a non-linear models.

Slide 8 Results: Specific Effects

Nothing passed multiple testing

Comment that I identified SOX30 in my Master´s project with

Slide 9 Database investigation of DMR genes

I interrogated this database with lists of the 22 significant genes from the Common Effects and genes with a nominal p-value 0.05 from the Specific Effects. I was able to query several databases at the same time, for GO terms and Reactome pathways.

Slide 10 SynGo

I identified GO terms annotated to synaptic processes – as I reported previously with SHANK2. In the interest of time, I will go ahead to

Slide 11 EpiFactors

EpiFactors provides a catalog of the enzymes, complexes and other factors that catalyze or regulate different types of epigenetic modifications.

Slide 12: Results Common

Genes associated with significant functions, modifications or targets. They are apparently involved in gene silencing.

In the hippocampus *KDM2B* represses WnT signalling genes which are crucial for proper neural development and morphogenesis (Zhang 2023)

Slide 13: Results Specific Olanz

Genes associated with phosphorylation with versatile functions like txt, DNA repair, replication

Slide 14: Results Specific Que

Genes associated with chromatin remodeling complexes

Slide 15: Results Specific Ris

Genes associated with transcriptionally active chromatin

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