



Characterization of Allele-Specific Alternative Splicing & Expression Events in Schizophrenia

Raymond Benitez¹, Rohan Chatterjee¹, Jonatan Hervoso^{1,2}, Xinshu (Grace) Xiao^{1,2,3}

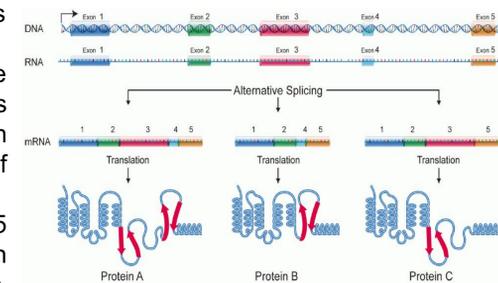
1 BIG Summer Program, Institute for Quantitative and Computational Biosciences, UCLA. 2 Bioinformatics Interdepartmental Program, UCLA. 3 Department of Integrative Biology and Physiology, UCLA

Abstract

RNA splicing is a highly regulated RNA processing mechanism, where introns are removed and exons are ligated to produce mature mRNA. Additionally, RNA splicing is a primary link between genetic variations and complex traits.³ RNA splicing is highly tissue specific, with a particularly high frequency and complex alternative splicing patterns in brain tissues. Many studies have shown that phenotypical changes in the prefrontal cortex are associated with schizophrenia. However, the genetic basis of dysregulated splicing in schizophrenia is not fully understood. Therefore, this study examined RNA-seq data from the Dorsolateral prefrontal cortex (DLPFC) of schizophrenia and control samples. We implemented the Allele Specific Alternative mRNA processing (ASARP) method, to identify genetically influenced Allele Specific Alternative Splicing (ASAS) events and Allele Specific Expression (ASE) events that contribute to schizophrenia. Our approach has identified several genes with allele specific expression and alternative splicing events. Our results provide an improved understanding of the genetically driven ASAS and ASE associated with schizophrenia.

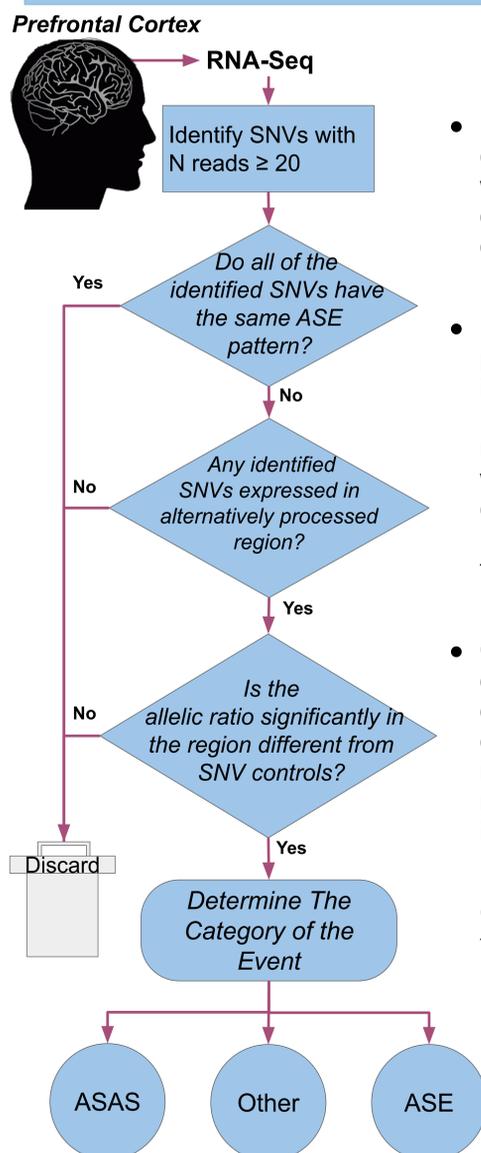
Background

- RNA splicing allows for formation of diverse functional mRNAs from a single transcript, which encode their own unique proteins.
- MBP is a gene responsible for coding proteins that create the myelin sheath for oligodendrocytes and Schwann cells. Studies have suggested that oligodendrocyte and myelin dysregulation could lead to cognitive dysfunction, a core characteristic of schizophrenia.⁴
- In this study we analyzed RNA-seq data from the DLPFC of 185 brain samples. With the goal of finding a relationship between alternative RNA splicing due to SNPs and schizophrenia. To do this we examined ASARP events in the samples.



Methodology

Allele Specific Alternative mRNA Processing Pipeline



BrainGVEX Dataset
93 Control Samples
92 Schizophrenia Samples

- First the proportions for each common gene in both cohort were calculated using the number of samples that a gene appears over a cohort.
- Proportion hypothesis tests were performed to test if the difference in the proportions was significant. Fisher's test was performed if number of times a gene appears was less than 5 in one of the cohorts. A significance level of .05 was chosen as the threshold for significance.

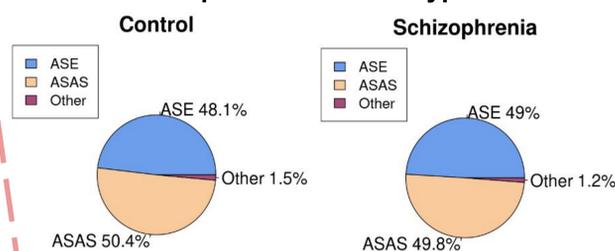
- Cohen's h was calculated to determine the effect size of the difference of the proportions. The effect size quantifies if the magnitude of the difference is meaningful. For any proportion p , its arcsin transformation is

$$\phi = \sqrt{2} \arcsin(p)$$

Given two proportions ϕ_1 and ϕ_2 , their effect size is:

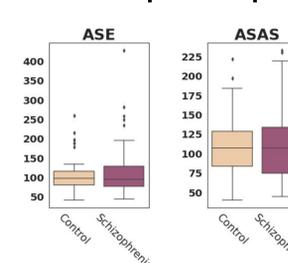
$$h = \phi_1 - \phi_2$$

Proportion of Event Types

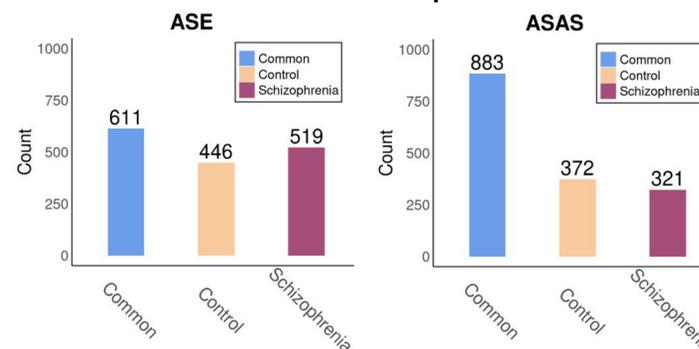


Both the proportion, on the left, and the event counts, on the right for ASE and ASAS were similar between cohorts.

Events per Sample

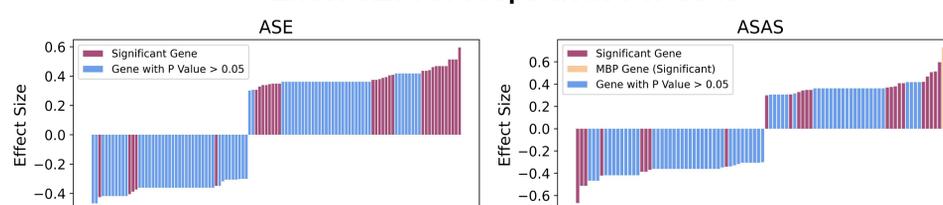


Gene Count Comparison

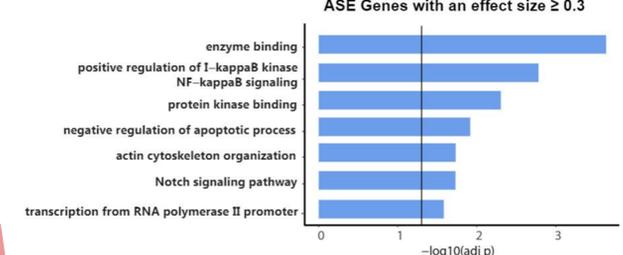
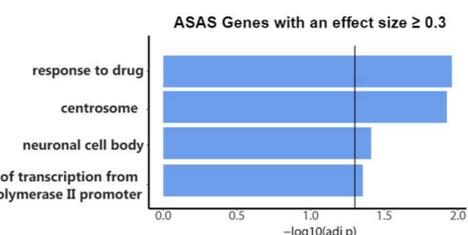


Counting the number of genes with ASE and ASAS events that are exclusive and common between cohorts

Effect Size For Proportions Per Gene

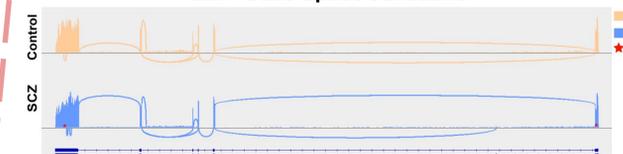


The effect size of the proportional differences is quantified using Cohen's H for each gene. All genes with a P-value < 0.05 and an effect size ≥ 0.3 were deemed significant.

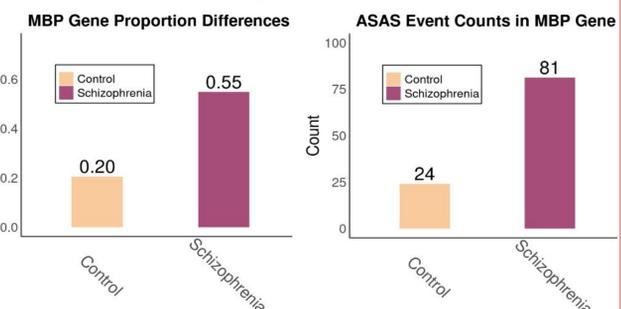


Gene Ontology revealed an enrichment in terms related to SCZ/Brain for genes with an effect size ≥ 0.3

MBP Gene Splice Junctions



An example of how ASAS events disrupt canonical splicing patterns



MBP had a higher proportion and count for ASAS events in schizophrenia compared to control.

Conclusions

- In this study we identified 25 genes with frequent ASAS events and 32 genes with frequent ASE events that are associated with Schizophrenia.
- MBP was observed to have a high occurrence of ASAS events in the schizophrenia cohort, suggesting that the production of myelin sheath for Schwann cells and oligodendrocytes may be disrupted in the disease.
- Similarly to Tkachev et al, we observe a disruption in the MBP gene associated with schizophrenia.⁵ Providing further insight into the mechanisms of the disease.

References

- Li Gang, et al. Identification of allele-specific alternative mRNA processing via transcriptome sequencing. Nucleic Acids Research. 2012
- Amoah Kofi, et al. Allele-specific alternative splicing and its functional genetic variants in human tissues. Genome Research. 2021
- Marina M. Scott, et al. RNA mis-splicing in disease. Nature Reviews Genetics. 2015
- Takahashi N, Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. Prog Neurobiol. 2011
- Dmitri Tkachev, et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet. 2003