Is maternal cigarette smoking connected to Neurodevelopmental Disorders in fetuses? An Analysis of Critical Genes Associated with Neurodevelopmental Disorders in Cord Blood Cells

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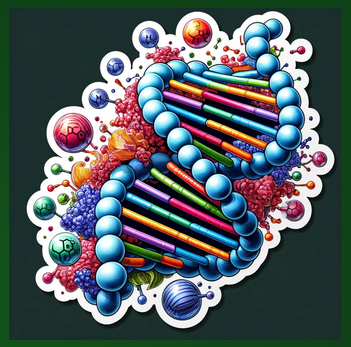


Introduction

- It has been shown that smoking during pregnancy detrimentally affects the fetus's brain development leading to neurodevelopmental disorders, but the mechanisms involved remain poorly understood.
- We aim to study DNA methylation, an epigenetic factor commonly correlated with transcriptional silencing.
- Cigarette smoke is a known environmental factor that impacts DNA methylation.
- We hypothesize that we will find abnormal methylation in DNA among fetuses exposed in-utero to cigarette smoke, specifically among DNA loci associated with neurodevelopmental disorders.

Methods

Volunteers Recruited

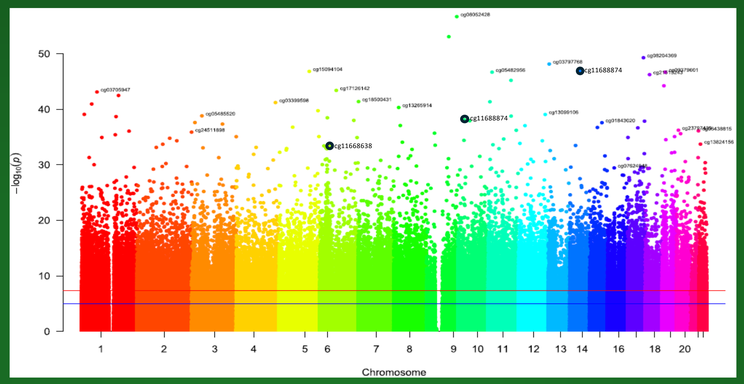
Case Control

Umbelicup® used to collect fetal cord blood cells after birth.

Blood processed at University of South Florida, Tampa. Isolated DNA and RNA for various studies.

Illumina 450k methylation array performed at Moffitt Cancer Center, USF, Tampa.

Results



This Manhattan plot helps visualize the significance of over 450,000 CpG sites in the DNA. The significance level of $10^{-7.5}$ is shown by the red line. Data points above this line are unlikely to not be associated with pregnant cigarette smoking. The tallest points are the most significant in our comparison between the case and control.

Gene Ontology (GO) and pathway enrichment of differentially methylated regions revealed processes of multicellular organ development, system development, and regulation of multicellular organismal processes. The disease annotation function analysis revealed that methylated genes can be mostly classified as Schizophrenia, Alzheimer's disease, and many cancer-related genes.

We used Open AI's GPT-4 to analyze the data related to Autism Spectrum Disorder (ASD). Using the AI data analysis tool, we updated old genes names, as the data for this study was obtained a few years ago. We compared our data to genes related to ASD according to Simons Foundation Autism Research Initiative (SFARI). This revealed that hundreds of significant sites in our data occurred on genes known to be causative factors in ASD.

The use of artificial intelligence in this analysis process proved invaluable. GPT-4 helped filter through nearly 39,000 significant CpG sites. 319 occur on genes which play a strong causative role in ASD, according to SFARI. A further 3,072 sites occur on genes that have been associated with ASD.

On the Manhattan plot, three CpG sites are circled. The tallest site in chromosome 10 is on the WAC gene which is strongly correlated with ASD. The site circled in chromosome 6 is on the PPP2R5D gene which is moderately correlated with ASD. The tallest site in chromosome 14, and the 9th tallest site overall in our epigenome wide association study (EWAS) is on the GPHN gene. This gene is a strong candidate for ASD risk.

Conclusion

- So far, the data has been supportive of our hypothesis; abnormal DNA methylation has occurred in genes associated with neurodevelopmental disorders.
- This study helps to build our understanding of the mechanisms underlying abnormal neurodevelopment, and other epigenetic effects of in-utero cigarette smoke exposure.
- Further research is being conducted into gene specific methylation analysis on the FMR1 gene, an X linked biomarker for ASD, because the sex chromosomes were not examined in this EWAS.