CS03-04 - HISTONE METHYLATION LANDSCAPES IN PREFRONTAL CORTEX REVEAL EPIGENETIC RISK ARCHITECTURES IN AUTISM AND SCHIZOPHRENIA

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Little is known about the molecular mechanisms governing developmentally regulated changes in gene expression and neuronal function during the maturation of human prefrontal cortex (PFC), including alterations in neuropsychiatric disease. Here, we separate neuronal and non-neuronal chromatin from postmortem PFC across the lifespan and map the genome-wide distribution of histone H3-trimethyl-lysine 4 (H3K4me3), an epigenetic mark associated with transcriptional regulation.

Methods: Neuronal nuclei from postmortem prefrontal cortex were immunotagged with NeuN antibody, and NeuN+ and NeuN- nuclei sorted separately via fluorescence-activated nuclei sorting, and purified mononuclesomes enriched for H3K4me3 analyzed by massively parallel sequencing. Neuronal H3K4me3 epigenomes were obtained from the PFC of control subjects from late prenatal to old age, and compared to epigenomes of subjects on the autism or schizophrenia spectrum.

Results: We present evidence for a highly regulated, 'pre-programmed' remodeling of histone methylation landscapes in immature PFC neurons that lasts at least into the early childhood years, involving hundreds of loci and a distinct set of transcription factors. Furthermore, histone methylation alterations in prefrontal neurons of diseased subjects were highly variable. As a group, loci with disease-associated H3K4me3 alterations showed a significant, 2-3 fold enrichment for genes associated with heritable risk for neurodevelopmental disease. We estimate that less than 5% of altogether 711 loci affected in our cohort of 16 autism subjects were related to a copy number variant at that site.

Conclusions: Taken together, these findings highlight the 'epigenetic vulnerability' of the immature PFC and point to significant overlap between the genetic and epigenetic risk architectures of major psychiatric disease.

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