A 01

CROSSTALK BETWEEN HISTONE MODIFICATIONS AND DNA METHYLATION IN PATIENTS WITH INTELLECTUAL DISABILITY DUE TO JARID1C MUTATIONS

B.H.Y. Chung[1,2], D. Grafodatskaya[1], D.T. Butcher[1], S.W. Scherer[1,3], F.E. Abidi[4], C.E. Schwartz[4], R. Weksberg[1]

[1]Genetics and Genome Biology, Division of Clinical & Metabolic Genetics, [3]The Centre for Applied Genomics, Hospital for Sick Children, Toronto ON, Canada, [4]Greenwood Genetic Center, South Carolina, USA.

The X-linked gene, *JARID1C*, encodes a H3K4 demethylase. Mutations in this gene cause intellectual disability (ID). We hypothesized that *JARID1C* mutations would dysregulate DNA methylation at specific genomic targets.

Method: A genome-wide approach was used to analyze sodium bisulfite modified genomic DNA from white blood cells of patients with known *JARID1C* mutations (n=13). The Illumina Methylation 27 Microarray with probes for 27,578 CpG sites covering >14,000 genes was used. DNA methylation profiles of patients were compared to sex- and age- matched controls. Differentially methylated CpG sites were identified using the Mann-Whitney test (absolute methylation difference >17% and p-value cut-off <0.05) with correction for multiple testing.

Results: Differential methylation analysis identified 17 genes with loss of CpG methylation. For 5 genes demonstrating the most significant loss of methylation in patients, the array findings were validated by pyrosequencing. Bioinformatic analyses showed that the DNA methylation alterations co-localized with the expected types of histone modifications in the target genes. CHIP-qPCR and expression array analyses, using lymphoblastoid cell lines from the same patients, are in progress.

Conclusion: Genes that function in epigenetic regulation play an important role in normal neurodevelopment. However, the molecular mechanisms by which multiple hierarchical epigenetic marks drive normal development are not well understood and the critical genomic targets are largely unknown. Therefore, disorders caused by mutations in genes that apply or remove epigenetic marks at specific genomic targets provide a unique opportunity to study the pathophysiology of epigenetic dysregulation in human disease. Our study has identified a specific pattern of DNA methylation alterations in patients with *JARID1C* mutations. These data demonstrate the functional specificity of these epigenetic regulators and also the cross-talk that occurs between histone modifications and DNA methylation in chromatin-mediated transcriptional regulation.