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Sent: Wed 7/29/15 1:15 PM

To: Shicheng Guo (shicheng.guo@hotmail.com)

CLEP-D-15-00093

Analysis of DNA methylation landscape reveals the roles of DNA methylation in the regulation of drug metabolizing enzymes

Clinical Epigenetics

Dear Dr. Guo,

I would like to invite you to review the manuscript above which has been submitted to Clinical Epigenetics. Further details including the full abstract can be found at the end of this email.

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Best wishes,

Trygve Tollefsbol, Ph.D., D.O.

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CLEP-D-15-00093

Research

Analysis of DNA methylation landscape reveals the roles of DNA methylation in the regulation of drug metabolizing enzymes

Clinical Epigenetics

Abstract: Background: Drug metabolizing enzymes (DMEs) exhibit dramatic inter- and intra-individual variability in expression and activity. However, the mechanisms determining this variability have not been fully elucidated. The aim of this study was to evaluate the biological significance of DNA methylation in the regulation of DME genes by genome-wide integrative analysis.

Results: DNA methylation and mRNA expression profiles of human tissues and hepatoma cells were examined by microarrays. The data were combined with GEO datasets of liver tissues, and integrative analysis was performed on selected DME genes. Detailed DNA methylation statuses at individual CpG sites were evaluated by DNA methylation mapping. From analysis of 20 liver tissues, highly variable DNA methylation was observed in 37 DME genes, 7 of which showed significant inverse correlations between DNA methylation and mRNA expression. In hepatoma cells, treatment with a demethylating agent resulted in upregulation of 5 DME genes, which could be explained by DNA methylation status. Interestingly, some DMEs were suggested to act as tumor-suppressor or housekeeper based on their unique DNA methylation features. Moreover, tissue-specific and age-dependent expression of UDP-glucuronosyl transferase 1A splicing variants was associated with DNA methylation status of individual first exons.

Conclusions: Some DME genes were regulated by DNA methylation, potentially resulting in inter- and intra-individual differences in drug metabolism. Analysis of DNA methylation landscape facilitated elucidation of the role of DNA methylation in the regulation of DME genes, such as mediator of inter-individual variability, guide for correct alternative splicing, and potential tumor suppressor or housekeeper.