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“Identification of endometrial cancer methylation features using a combined methylation analysis method”

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Biomedical Research Tower 105
11am
VITA

June 2002
North Olmsted High School

June 2006
B.S. Microbiology, Minor in Chemistry, The Ohio State University

June 2007 to present
Graduate Research Associate, Biomedical Graduate Program, The Ohio State University

COMMITTEE MEMBERS

Joanna L Groden, Advisor
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ABSTRACT

Introduction: DNA methylation is a stable epigenetic mark often perturbed during carcinogenesis. Growing evidence demonstrates a role for DNA methylation both as a regulator of gene expression and as a potential biomarker. Widespread accumulation of methylation in regulatory elements in certain cancers (termed the CpG island methylator phenotype) may play a role in carcinogenesis. Few studies, however, have examined the CpG island methylator phenotype genome-wide in a clinical cohort, as until recently analyzing methylation genome-wide in a large number of samples was cost prohibitive. As a result, the methodology for analyzing these large datasets remains poorly developed.

Methods: This project profiled the methylomes of 76 sporadic endometrioid endometrial primary tumors and 12 normal endometrial samples using methylated fragment capture followed by second generation sequencing (MethylCap-seq). A public dataset of 203 endometrioid endometrial tumors from The Cancer Genome Atlas (TCGA), profiled using the Infinium HumanMethylation 450 beadchip, was also examined. A MethylCap-seq quality control module was developed to exclude sequencing samples with poor-quality methylation data. Additional MethylCap-seq datasets were also used to develop and validate the quality control module.

Results: The quality control module significantly improved methylation calls, resulting in reduced noise in methylation signal and improved ability to resolve differentially methylated regions. To identify hypermethylator tumors, an analytic method was developed that defines a hypermethylator phenotype using MethylCap-seq and uses Infinium to generate a representative methylation signature.
that can be tested with non-genome-wide approaches. In the MethylCap-seq discovery set, analysis of genome-wide methylation in promoter CpG islands (CGI) identified a subset of tumors with a methylator phenotype. To identify hypermethylator tumors in other cohorts, a 13-region methylation signature composed of Infinium probes was developed and validated using a training set of five highly methylated and eight control tumors. In the TCGA test set, high signature methylation score was associated with mismatch repair deficiency, high mutation rate, and low somatic copy number alteration. In addition, the method proved highly robust, showing good agreement with previously published methylation clusters for the test set as well as consistent ranking of tumors across alternative signatures. Furthermore, the methylation signature distinguished >90% of endometrioid endometrial tumors from normal controls.

**Conclusion:** A methylation signature has been developed that should aid in identifying and characterizing the hypermethylator phenotype in endometrial cancer. This study also illustrates a novel methodology that could prove useful for identifying extreme methylation phenotypes in other cancers. Further studies should increase understanding of methylation perturbations in cancer, and could lead to better detection and treatment of hypermethylator tumors.
RECENT PUBLICATIONS


AWARDS AND HONORS

2013-2015  Choose Ohio First Scholarship. Ohio’s STEMM Ability Alliance, Ohio Department of Education
2011-2013  Mentored Research Training Fellowship (TL1). OSU Center for Clinical & Translation Sciences, National Center for Research Resources
2010       Clinical and Translational Science Award: Best Clinical & Translational Abstract. Trimarchi M.P., Powell N.D., Sheridan J.F. Social Stress Effects on Asthma: A Role for Osteopontin. The Ohio State University Oral Biology Research Day, Columbus, Ohio
2008-2009  Research Graduate Fellowship (T32). Training Program in Integrative Immunobiology (Virginia M. Sanders, PI), National Institute of Allergy and Infectious Diseases