

Insights & Perspectives

Illuminating Epigenetic Changes with the GoldenGate® Assay for Methylation

In the past few decades, much has been discovered about the genetic basis of cancer—how mutations in the DNA coding sequences of cancer-related genes can cause cells to divide uncontrollably, resulting in tumors. However, much less is known about the epigenetic basis of cancer. Epigenetic changes do not affect the genetic code of DNA but rather influence the interactions of DNA bases with proteins that control gene expression. Illumina® recently introduced a product that can detect the methylation of cytosine bases in DNA, a very important type of epigenetic change. This product, the GoldenGate Assay for Methylation, is the only assay on the market that can simultaneously analyze over 1,500 potential methylation sites in DNA with a fast turn around time, high sensitivity, and excellent reproducibility.

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The most common targets for DNA methylation are cytosines in CpG dinucleotides, which occur in clusters called “CpG islands” in the regulatory regions of many genes. Aberrant CpG methylation has been linked to cancer as well as other diseases

such as multiple sclerosis, diabetes, and schizophrenia. For example, hypermethylation of CpG islands in the promoter regions of tumor suppressor genes is the most frequent means of gene inactivation in cancer.

Illumina’s GoldenGate Assay for Methylation detects CpG methylation by treating genomic DNA with bisulfite, which converts unmethylated cytosines (but not methylated cytosines) to uracils. Bisulfite-treated CpG islands are amplified, fluorescently labeled, and hybridized to a Sentrix® Array Matrix (SAM) to simultaneously and quantitatively analyze the methylation status of up to 1,536 different CpG sites. As in Illumina’s other BeadArray™ products, each sequence in the methylation platform is present at an average 30-fold redundancy, which greatly increases the sensitivity and reproducibility of detection. The GoldenGate Methylation Cancer Panel I includes CpG loci from over 800 genes, including tumor suppressor genes, oncogenes, and genes involved in DNA repair, cell cycle control, cell differentiation, and apoptosis. All of the genes in the Cancer Panel I are also represented on the Illumina Human-6 v2 Expression BeadChip, allowing cross-application analyses. For example, researchers can compare CpG methylation status with gene expression for a particular tumor suppressor gene from a biopsy sample. Researchers can also order custom panels from Illumina that contain specific CpG sites of interest. The high-throughput capacity of the Illumina GoldenGate Assay for Methylation differenti-



DR. BRIAN REID, M.D., Ph.D. and researcher PATRICIA GALIPEAU of the Fred Hutchinson Cancer Research Center at the University of Washington have used the GoldenGate Assay for Methylation to study DNA methylation changes in Barrett’s esophagus.

ates it from other commercially available methylation assays. In addition to allowing simultaneous analysis of 1,536 CpG sites, 96 different DNA samples (e.g., from different tumor biopsies or cell lines) can be analyzed per array. Furthermore, the assay is quick and relatively simple to complete, with a three-day workflow. Thus, the GoldenGate Assay for Methylation is expected to greatly accelerate research in the field of DNA methylation.

Dr. Brian Reid and Patricia Galipeau of the Fred Hutchinson Cancer Research Center have used the GoldenGate Assay for Methylation to study DNA methylation changes in Barrett's esophagus. Barrett's esophagus is a condition in which chronic acid reflux causes esophageal injury, leading to replacement of the normal squamous cell lining of the esophagus with an abnormal lining called specialized intestinal metaplasia. Five to ten percent of patients with Barrett's esophagus develop a form of cancer called esophageal adenocarcinoma. Reid and Galipeau are using the GoldenGate Assay for Methylation to compare CpG site methylation in patients with benign and cancerous Barrett's esophagus, with the ultimate goal of predicting which Barrett's patients will develop cancer on the basis of the methylation status of key CpG islands. According to Galipeau, "The GoldenGate Assay for Methylation is the only genome-wide, high-capacity methylation technology that's currently available for these types of studies."

In addition to high sensitivity and reproducibility, the flexibility of the GoldenGate Assay platform is important to Reid and Galipeau. Reid says, "We wanted to study genome-wide methylation in Barrett's esophagus, but the limiting factor was that prior to the GoldenGate Assay for Methylation, there was really nothing that could easily transition

from a discovery phase into the clinic." Galipeau adds, "Illumina has made their technology flexible in a way that it can be used for discovery research and also for translation research. Illumina has a robust technology that can transition into a type of application that will ultimately benefit patients." The researchers stress that the simplicity of the GoldenGate Assay for Methylation may someday enable its use in hospitals around the country, without the need for extremely expensive equipment or highly trained technicians.

The accuracy, speed, simplicity, and flexibility of the GoldenGate Assay for Methylation make it a valuable new tool for genome-wide methylation profiling.

Reid predicts that the GoldenGate Assay for Methylation will aid in the understanding of how epigenetic changes such as aberrant methylation interact with genetic abnormalities to facilitate cancer progression. This knowledge will aid in cancer diagnosis, prognosis, and treatment. Reid says, "Once we know how methylation and genomic changes interact, biomarker panels for predicting risk will improve. Also, you might be able to combine treatments to slow down cancer progression by targeting both genetic and epigenetic pathways." The accuracy, speed, simplicity, and flexibility of the GoldenGate Assay for Methylation make it a valuable new tool for genome-wide methylation profiling.

—by **Laura Cassiday, Ph.D.**
(lauracassiday@yahoo.com), a freelance writer in Hudson, Colorado.

ADDITIONAL INFORMATION

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This newsletter is dedicated to publishing news, perspectives, and insights about and for the Illumina Community. We are committed to providing you with the content you want to see as a member of the Illumina Community. Please email me with suggestions for topics you'd like to read about at icommunity@illumina.com. —Lori Lebruska, Ph.D., Editor.

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