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Low-cost, Comprehensive Methylation Profiling Using Low DNA Inputs for Cancer Diagnostics

Stanford researchers have developed a new, low-cost method for tumor methylation profiling that enables tumor classification even from low amounts of fragmented DNA characteristic of liquid biopsies.

Methylation profiling has emerged as a critical tool in the diagnosis and classification of cancer. The abnormal patterns of gene methylation found in cancer cells can enable early diagnosis, cancer type classification, prognosis assessment, and treatment monitoring. However, available methods for classifying methylation status are lacking. Whole genome bisulfite sequencing is prohibitively costly, while methylation arrays are limited by a requirement for high amounts of input DNA and poor overlap with cell-type markers critical for tumor classification. Other methods are also not suited for the fragmented DNA and low tumor cellularity found in many biopsies.

Stanford researchers therefore developed a new method for methylation classification ("XR-methylseq") that is low cost, unbiased, enables tumor type classification, and suitable for low, fragmented DNA inputs (down to 250 pg). DNA fragments are ligated to an adapter, digested with a restriction enzyme at CCGG motifs, and ligated to a second adapter. Fragments are enzymatically converted to distinguish methylation status and only fragments with both adapters are amplified and sequenced. Researchers demonstrated that this technique can accurately classify CNS tumors from CSF, which is not possible using other methods due to the low DNA content and tumor cellularity found in CSF.

Stage of Development
Proof of concept: XR-methylseq enables tumor classification from CSF

Applications

- Analysis of both solid and liquid biopsies (e.g., urine, CSF, biopsy supernatant)
- Diagnosis and classification of cancer
- Early cancer detection
- Prediction of cancer prognosis
- Personalized cancer treatment
- Minimal residual disease testing
- Monitoring of treatment response and resistance
- Basic research into methylation profiles

Advantages

- Overlaps with cell type markers to enable tumor classification
- Uses enzymatic digestion instead of harsh bisulfite chemistries that break DNA
- Works with low DNA inputs (250 pg) and low tumor cellularity
- Low cost
- Works with fragmented DNA often seen in biopsies
- Highly correlated with WGBS gold standard (not biased)
- 95%+ on-target rate, leading to an 18-fold enrichment at CCGG flanks

Patents

- Published Application: WO2025106807

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