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DNA methylation-based testing to classify central nervous system tumors

Despite being the mainstay of pathology tissue diagnostics, microscope-based histological review has limitations. Among them is that pathologists may have differing opinions about a case. This interobserver variability may result in over- or undertreatment of the patient and lack of agreement about which diagnosis is correct. Another limitation occurs when pathologists diagnose by classifying tumors into discrete categories based on well-defined features, supported by evidence, and a tumor is not an exact fit for a category. To improve objectivity and reproducibility and uncover new information about tumors, the medical community is beginning to move toward large-scale analytical platforms. These platforms have helped refine microscope diagnostics and improved understanding of new molecular and biological features of tumors that could be useful in classification and therapy. The authors of this study used a DNA methylation platform to classify central nervous system (CNS) tumors in adults and children. DNA methylation is an epigenetic change in which methyl (CH3) groups are added or removed from the DNA to alter gene expression. The underlying DNA strand remains unchanged, but it is modified in a reversible way. Methylation occurs during cell line-specific development and tumor development, making DNA methylation signatures a potential biomarker platform for grouping tumors into reproducible clusters. Using Infinium HumanMethylation450K BeadChip arrays, the authors first developed a reference DNA methylation database of 76 unique histopathological entities, which included primary CNS tumors and other common CNS malignancies, such as lymphoma and melanoma. Analysis of these signatures resulted in 82 methylation classes. The authors also sampled seven normal CNS regions to develop an additional nine methylation classes. Further analysis of these methylation groups identified eight “methylation class families” that shared histopathologically and biologically closely related tumors. Once the reference database was complete, the authors prospectively profiled 1,155 diagnostic CNS adult and pediatric tumor cases. Seventy-six percent of the tumors represented categorized entities, while the remainder did not match the histological profile. These latter cases were rereviewed using light microscopy and additional testing and resulted in a change in diagnosis in 12 percent of the overall cases. One percent of the overall cases could not be resolved and four percent could not be tested due to low tumor content. After obtaining these results, the authors collaborated with five external centers to set up testing at their sites. These sites showed robust interlaboratory correlation of testing and also had a 12 percent misclassification rate when using light microscopy alone, suggesting methylation profiling may increase the ability to classify CNS tumors. To disseminate the platform, the authors set up a free web-based tool for data analysis and report generation at www.molecularneuropathology.org. The use of DNA methylation profiles in the setting of machine learning and automated platforms may be of value in analyzing CNS tumors in children and adults. Although some tumor categories did not have a large number of samples, the authors intend to use ongoing data uploads to streamline their classifiers and improve diagnostic prediction. While many tumors can map back to known World Health Organization categories, a large group of new or variant tumors may require further investigation. Ongoing study of methylation-based platforms may modify the diagnosis of CNS tumors and, perhaps, many other tumor types in future years.

Capper D, Jones DTW, Sill M, et al. DNA methylation-based classification of central nervous system tumours. *Nature.* 2018;555:469–474.doi:10.1038/nature26000.

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Use of models to predict environmental metabolome from metagenomics

The human microbiome, which represents the combined genetic material of all bacteria in unique locations within the body, has been emerging as a key factor in determining human health and disease. Bacteria are so prevalent in our bodies that their combined genetic material far outweighs the number of our genes. Many locations, such as the gut, can have hundreds of distinct bacterial species coexisting. While the study of individual bacteria is relatively straightforward in the laboratory environment, understanding how hundreds of bacteria coexist and how their collective effects alter the microenvironment in a specific location in the body is more challenging. Yet understanding this relationship is important because bacterial changes in the microenvironment may reflect disease processes, as has been shown for colorectal cancer. The authors addressed this challenge by combining genome-scale metabolic models (GSMMs) and predicted in silico growth modeling in various environmental conditions to predict the environmental metabolome in specific body sites. They used shotgun metagenomics to assess the bacterial composition and genomic content of the microenvironment and combined this with GSMMs of each species to predict the metabolic environment that would allow the unique bacterial populations to coexist. GSMMs infer the metabolic output of each bacterium by analyzing how predicted protein expression networks would interact. The authors next determined the optimal microenvironmental conditions that would lead to these bacterial combinations seen through metagenomics. This approach, called Metabolomic Analysis of Metagenomes using fBa and Optimization (MAMBO), was successful in determining the metabolic environment of the vagina, mouth, skin, and stool. Furthermore, MAMBO could predict the metabolomes when provided with publicly available input metagenomics data from the Human Microbiome Project. By comparison, the use of metagenomics alone, without GSMMs or optimization, could not predict the metabolome. The development of a rapid, large-scale approach to predicting the metabolome is important for predicting bacterial compositions that may fluctuate with human health and disease. Whether the production of metabolites by these bacteria may also have secondary effects is still being investigated. The ability to rapidly model the bacterial microenvironment and predict bacterial metabolism may further understanding of bacteria in the human body.

Garza DR, van Verk MC, Huynen MA, et al. Towards predicting the environmental metabolome from metagenomics with a mechanistic model. *Nat Microbiol.* 2018;3:456–460. doi:10.1038/S41564-018-0124-8.

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