DNA methylation

- Methylation Status of the Telomerase Reverse Transcriptase Promoter in Parotid Tumours and Adjacent Parotid Gland Tissue: A Pilot Study on the Implications for Recurrence and Development of Malignancy
- beta-Mangostin Attenuates TET2-Mediated DNA Demethylation of Prkcg in the Prevention of Intervertebral Disc Degeneration
- Multi-Omics Perspectives on Testicular Aging: Unraveling Germline Dysregulation, Niche Dysfunction, and Epigenetic Remodeling
- ARID4B: An Orchestrator from Stem Cell Fate to Carcinogenesis
- Genetics and Epigenetics of Chemoinduced Oral Mucositis in Paediatric Patients with Haematological Malignancies-A Review
- Prenatal Delta-9-Tetrahydrocannabinol Exposure Induces Transcriptional Alterations in Dopaminergic System with Associated Electrophysiological Dysregulation in the Prefrontal Cortex of Adolescent Rats
- DNA Methylation, Aging, and Cancer
- Epigenetic DNA Methylation Under the Influence of Low-Dose Ionizing Radiation, and Supplementation with Vitamin B12 and Folic Acid: Harmful or Beneficial for Professionals?

DNA methylation is an epigenetic modification in which a methyl group (CH3) is attached to cytosine, a nucleobase in human DNA. Appropriately controlled DNA methylation leads to proper regulation of gene expression. However, abnormal gene expression that departs from controlled genetic transcription through aberrant DNA methylation may occur in cancer or other diseases.

Methylation can change the activity of a DNA segment without changing the sequence. When located in a gene promoter, DNA methylation typically acts to repress gene transcription. DNA methylation is essential for normal development and is associated with a number of key processes including genomic imprinting, X-chromosome inactivation, repression of transposon elements, aging and carcinogenesis.

One of the first and most important epigenetic modifications studied in humans is DNA methylation, which describes the covalent addition of a methyl group preferentially at the 5′-position of a cytosine or guanine nucleotide. These CpG dinucleotides tend to cluster to so-called CpG islands, being located in the promoter regions of more than half of all human genes, or to CpG island shores, which are regions of lower CpG density that lie in close proximity to CpG islands [1) 2)].

DNA methylation inhibitor

DNA methylation inhibitor.

DNA methylation in neurosurgery

In each glioblastoma GBM, hundreds of genes are subject to DNA hypermethylation at their CpG island promoters. A subset of GBMs is also characterized by locus-specific and genome-wide decrease

in DNA methylation, or DNA hypomethylation.

DNA Methylation of the PDGFD Gene Promoter Increases the Risk for Intracranial Aneurysms and Brain Arteriovenous Malformations [3].

Childhood pilocytic astrocytomas (PA) are low grade tumours with an excellent prognosis. However, a minority, particularly those in surgically inaccessible locations, have poorer long term outcome. At present it is unclear whether anatomical location in isolation, or in combination with underlying biological variation, determines clinical behaviour. Here we have tested the utility of DNA methylation profiling to inform tumour biology and to predict behaviour in paediatric PA. Genome-wide DNA methylation profiles were generated for 117 paediatric PAs. Using a combination of analyses we identified DNA methylation variants specific to tumour location and predictive of behaviour. Receiver operating characteristic analysis was used to test the predictive utility of clinical and/or DNA methylation features to classify tumour behaviour at diagnosis. Unsupervised analysis distinguished three methylation clusters associated with tumour location (cortical, midline, and infratentorial). Differential methylation of 5,404 sites identified enrichment of genes involved in 'embryonic nervous system development'. Specific hypermethylation of NEUROG1 and NR2E1 was identified as a feature of cortical tumours. A highly accurate method to classify tumours according to behaviour, that combined three clinical features (age, location and extent of resection) and methylation level at a single site, was identified. Our findings show location-specific epigenetic profiles for PAs, potentially reflecting their cell type of origin. This may account for differences in clinical behaviour according to location independent of histopathology. We also defined an accurate method to predict tumour behaviour at diagnosis. This warrants further testing in similar patient cohorts [4].

Classification

DNA methylation classification is the process of categorizing methylation patterns in DNA based on their location, function, and regulatory impact. DNA methylation typically involves the addition of a methyl group to the 5' carbon of cytosine residues, commonly in CpG dinucleotides. Below are the major categories and criteria for classifying DNA methylation:

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1. Based on Genomic Context - **CpG Islands (CGIs):**

1. Regions of DNA with a high frequency of CpG sites.
2. Found near promoter regions of genes.
3. Hypermethylation can lead to gene silencing.

- **Non-CpG Islands:**

1. Found in gene bodies, intergenic regions, or repetitive elements.
2. Non-CpG methylation is more common in specific cell types (e.g., neurons).

- **Repetitive Elements:**

1. Includes LINEs, SINEs, and transposable elements.
2. Methylation suppresses transposition and maintains genomic stability.

- **Enhancers and Regulatory Regions:**

1. Methylation in these regions can alter enhancer activity and gene regulation.

- **Gene Bodies:**

1. Methylation in the gene body can influence transcription elongation and splicing.

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2. Based on Function - **Epigenetic Regulation:**

1. Gene silencing through promoter methylation.
2. X-chromosome inactivation (e.g., in females).
3. Genomic imprinting to regulate parent-of-origin expression.

- **Genomic Stability:**

1. Prevents expression of transposable elements.
2. Maintains chromosomal integrity.

- **Cell Differentiation and Development:**

1. Establishes cell-specific methylation patterns.

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3. Based on Cell Type or Developmental Stage - **Somatic Cells:**

1. Tissue-specific methylation patterns that contribute to cell identity.

- **Germline Cells:**

1. Methylation is reset during germ cell development, followed by re-establishment.

- **Cancer Cells:**

1. Global hypomethylation (genomic instability) and regional hypermethylation (tumor suppressor silencing).

- **Pluripotent Stem Cells:**

1. Low levels of methylation allow for greater transcriptional flexibility.

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4. Based on Stability - **Stable Methylation Marks:**

1. Persist through cell division and are heritable across generations.

- **Dynamic Methylation Marks:**

1. Reversible in response to environmental cues (e.g., diet, stress, toxins).

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5. Based on Technology Classification may also depend on how methylation is analyzed: - **Whole-Genome Bisulfite Sequencing (WGBS):**

1. Provides single-base resolution across the genome.

- **Reduced Representation Bisulfite Sequencing (RRBS):**

1. Focuses on CpG-dense regions.

- **Methylated DNA Immunoprecipitation Sequencing (MeDIP-seq):**

1. Captures methylated regions with an antibody.

- **Array-Based Methods:**

1. Such as Illumina Infinium BeadChips (e.g., EPIC arrays), for targeted CpG analysis.

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6. Based on Disease Association - **Oncogenic Methylation Patterns:**

1. Methylation of tumor suppressor genes or activation of oncogenes.

- **Neurological Disorders:**

1. Altered methylation in genes like MECP2 in Rett syndrome or environmental impacts in neurodevelopmental disorders.

- **Metabolic Disorders:**

1. Methylation affecting genes in metabolic pathways (e.g., obesity, diabetes).

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Applications: DNA methylation classification is essential for: - **Epigenetic research**: Understanding how genes are regulated. - **Biomarker discovery**: Identifying methylation patterns associated with diseases. - **Therapeutic targeting**: Developing drugs like DNA methyltransferase inhibitors.

Diagnostic impact studies

The aim of a study is to share the experience using DNA methylation classification in daily routine practice, illustrated through clinical cases. They employed a classification system to evaluate discrepancies between histo-molecular and DNA methylation diagnoses, with a specific focus on adult versus pediatric CNS tumors. In a study, they observed that 40% of cases fell into Class I, 47% into Class II, and 13% into Class III among the “matched cases” (≥ 0.84). In other words, DNA methylation classification confirmed morphological diagnoses in 63% of adult and 23% of pediatric cases. Refinement of diagnosis was particularly evident in the pediatric population (65% vs. 21% for the

adult population, p = 0.006). Additionally, they discussed cases classified with low calibrated scores. In conclusion, the study confirms that DNA methylation classification provides significant added-value for CNS tumors diagnosis, particularly in pediatric cases [5)]

This study reinforces the importance of integrating molecular techniques like DNA methylation classification into routine neuropathological practice. It serves as evidence of the method's potential to enhance diagnostic precision, particularly for complex or ambiguous cases.

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