# DNA methylation-based meningioma classification

DNA methylation patterns delineate clinically relevant subgroups for meningioma classification.

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Case series provide the support that tumor DNA methylation profiling adds meaningful meningioma classification information and may be beneficial to incorporate in clinical practice. The report also reveals that DNA methylation combined with WHO histology classification can more accurately predict tumor behavior than WHO classification alone [1)]

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Paramasivam et al., previously established the six meningioma methylation classes (MC) benign 1-3, intermediate A and B, and malignant.

They set out to identify subgroup-specific mutational patterns and gene regulation. Whole genome sequencing was performed on 62 samples across all MCs and WHO grades from 62 patients with matched blood control, including 40 sporadic meningiomas and 22 meningiomas arising after radiation (Mrad). RNA sequencing was added for 18 of these cases and chromatin-immunoprecipitation for histone H3 lysine 27 acetylation (H3K27ac) followed by sequencing (ChIP-seq) for 16 samples. Besides the known mutations in meningioma, structural variants were found as the mechanism of NF2 inactivation in a small subset (5%) of sporadic meningiomas, similar to previous reports for Mrad. Aberrations of DMD were found to be enriched in MCs with NF2 mutations, and DMD was among the most differentially upregulated genes in NF2 mutant compared to NF2 wild-type cases. The mutational signature AC3, which has been associated with defects in homologous recombination repair (HRR), was detected in both sporadic meningioma and Mrad, but widely distributed across the genome in sporadic cases and enriched near genomic breakpoints in Mrad. Compared to the other MCs, the number of single nucleotide variants matching the AC3 pattern was significantly higher in the malignant MC, which also exhibited higher genomic instability, determined by the numbers of both large segments affected by copy number alterations and breakpoints between large segments. ChIP-seq analysis for H3K27ac revealed a specific activation of genes regulated by the transcription factor FOXM1 in the malignant MC. This analysis also revealed a super enhancer near the HOXD gene cluster in this MC, which, together with general upregulation of HOX genes in the malignant MC, indicates a role of HOX genes in meningioma aggressiveness. This data elucidates the biological mechanisms rendering different epigenetic subgroups of meningiomas, and suggests leveraging homologous recombination repair (HRR) as a novel therapeutic target [2)].

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In a study, Sahm et al., aimed for a comprehensive characterisation of the entire molecular genetic landscape of meningioma to identify biologically and clinically relevant subgroups.

In this multicentre, retrospective analysis, they investigated genome-wide DNA methylation patterns of meningiomas from ten European academic neuro-oncology centres to identify distinct methylation classes of meningiomas. The methylation classes were further characterised by DNA copy number analysis, mutational profiling, and RNA sequencing. Methylation classes were analysed for

progression-free survival outcomes by the Kaplan-Meier method. The DNA methylation-based and WHO classification schema were compared using the Brier prediction score, analysed in an independent cohort with WHO grading, progression-free survival, and disease-specific survival data available, collected at the Medical University Vienna (Vienna, Austria), assessing methylation patterns with an alternative methylation chip.

They retrospectively collected 497 meningiomas along with 309 samples of other extra-axial skull tumours that might histologically mimic meningioma variants. Unsupervised clustering of DNA methylation data clearly segregated all meningiomas from other skull tumours. We generated genome-wide DNA methylation profiles from all 497 meningioma samples. DNA methylation profiling distinguished six distinct clinically relevant methylation classes associated with typical mutational, cytogenetic, and gene expression patterns. Compared with WHO grading, classification by individual and combined methylation classes more accurately identifies patients at high risk of disease progression in tumours with WHO grade I histology, and patients at lower risk of recurrence among WHO grade II tumours (p=0·0096) from the Brier prediction test). We validated this finding in our independent cohort of 140 patients with meningioma.

DNA methylation-based meningioma classification captures clinically more homogenous groups and has a higher power for predicting tumour recurrence and prognosis than the WHO classification. The approach presented here is potentially very useful for stratifying meningioma patients to observation-only or adjuvant treatment groups. We consider methylation-based tumour classification highly relevant for the future diagnosis and treatment of meningioma [3].

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