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 HRR as a novel therapeutic target [1].

1)
Paramasivam N, Hübschmann D, Toprak UH, Ishaque N, Neidert M, Schrimpf D, Stichel D, Reuss D, Sievers P, Reinhardt A, Wefers AK, Jones DTW, Gu Z, Werner J, Uhrig S, Wirsching HG, Schick M, Bewerunge-Hudler M, Beck K, Brehmer S, Urbschat S, Seiz-Rosenhagen M, Hänggi D, Herold-Mende C, Ketter R, Eils R, Ram Z, Pfister SM, Wick W, Weller M, Grossmann R, von Deimling A, Schlesner M, Sahm F. Mutational patterns and regulatory networks in epigenetic subgroups of meningioma. Acta Neuropathol. 2019 May 8. doi: 10.1007/s00401-019-02008-w. [Epub ahead of print] PubMed PMID: 31069492.