Göteborg, 2022

DNA methylation profiling of CNS tumors; implications for clinical diagnostics

Akademisk avhandling
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson,
Medicinaregatan 3, Göteborg, fredagen den 28 oktober 2022, klockan 9.00.
av **Sandra Ferreyra Vega**

Fakultetsopponent:

Professor Bjarne Winther Kristensen,

University of Copenhagen, Denmark

Avhandlingen baseras på följande delarbeten

I. **Ferreyra Vega S,** Olsson Bontell T, Corell A, Smits A, Jakola AS, Carén H. DNA methylation profiling for molecular classification of adult diffuse lower-grade gliomas. *Clinical Epigenetics*, 2021, 13(1):102.

II. Wenger A**, Ferreyra Vega S,** Kling T, Olsson Bontell T, Jakola AS, Carén H. Intratumor DNA methylation heterogeneity in glioblastoma: implications for DNA methylation-based classification. *Neuro-Oncology,* 2019, 21(5):616-27.

III. **Ferreyra Vega S,** Wenger A, Kling T, Olsson Bontell T, Jakola AS, Carén H. Spatial heterogeneity in DNA methylation and chromosomal alterations in diffuse gliomas and meningiomas. *Modern Pathology,* 2022, 1-11.

IV. **Ferreyra Vega S,** Olsson Bontell T, Kling T, Jakola AS, Carén H. Longitudinal DNA methylation analysis of adult-type *IDH*-mutant gliomas. *Manuscript.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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DNA methylation profiling of CNS tumors; implications for clinical diagnostics

Sandra Ferreyra Vega

Department of Clinical Neuroscience, Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract

Diffuse gliomas and meningiomas are the most common primary tumors of the central nervous system (CNS) in adults and cause a significant morbidity and mortality worldwide. DNA methylation is an epigenetic mechanism that controls gene expression and its dysregulation plays an important role in cancer. In this thesis, we evaluated the use of DNA methylation profiling for patient diagnosis and prognosis and further investigate intratumor methylation heterogeneity and its effects on the clinical diagnostics. In **Paper I**, we used DNA methylation profiling for molecular classification of diffuse lower-grade gliomas and showed its value as a tool for clinical diagnostics and prognostics of these tumors. In **Paper II**, we studied DNA methylation profiles across distinct regions of grade 4 glioblastomas and found methylation subclass differences within the tumors as well as variable methylation status of the clinical biomarker *MGMT*. In **Paper III**, we further showed DNA methylation heterogeneity within *IDH*-mutant gliomas and meningiomas and chromosomal copy number variability of the grading biomarker *CDKN2A/B* in *IDH*-mutant gliomas after accounting for varying tumor cell content. In **Paper IV**, we investigated DNA methylation changes during progression of *IDH*-mutant gliomas and showed that methylation profiles were mostly maintained upon recurrence.

In conclusion, we showed that DNA methylation profiling can be used for diffuse glioma diagnostics and prognostics. We further demonstrated the intratumor methylation and chromosomal heterogeneity in diffuse gliomas and meningiomas, which should be considered for the clinical diagnosis and treatment management of these patients.

Keywords: DNA methylation, diffuse gliomas, meningiomas, clinical diagnostics, heterogeneity

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