Göteborg, 2023

Improving diagnosis of central nervous system tumours using genetic and epigenetic tools

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Åke Göransson, Medicinaregatan 11, Göteborg, fredagen den 2 juni 2023 klockan 13.00.

av **Thomas Olsson Bontell**

Fakultetsopponent:

Professor Martin Hallbeck, Linköpings Universitet, Sverige

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. *Clin Epigenetics 2021:13(1):102*.

II. Ferreyra Vega S, **Olsson Bontell T**, Teresia K, Jakola AS, Carén H. Longitudinal DNA methylation analysis of adult-type *IDH*-mutant gliomas. *Acta Neuropathologica Communications 2023:11(1):23*.

III. Dénes A*, **Olsson Bontell T***, Barchéus H, Ferreya Vega S, Carén H, Lindskog C, Jakola AS, Smits A. The Clinical value of proneural, classical and mesenchymal protein signatures in WHO 2021 adult-type diffuse lower-grade gliomas. *Manuscript submitted*. *Shared first author.

IV. Deland L, Keane S, **Olsson Bontell T**, Fagman H, Sjögren H, Lind AE, Carén H, Tisell M, Nilsson JA, Ejeskär K, Sabel M, Abel F. Novel *TPR::ROS1* Fusion Gene Activates MAPK, PI3K and JAK/STAT Signaling in an Infant-type Pediatric Glioma. *Cancer Genomics Proteomics 2022:19(6):711-726.*

V. **Olsson Bontell T**, Danielsson A, Dahr N, Deland L, Tisell M, Sjögren H, Sabel M, Carén H, Abel F. Formation of ganglion cells in a nodular component of a cystic infratentorial pilocytic astrocytoma carrying *KIAA1549::BRAF* fusion. *Manuscript*.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

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Improving diagnosis of central nervous system tumours using genetic and epigenetic tools

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Abstract

Brain tumor diagnostics has traditionally been based on histopathology stains. The introduction of immunohistochemistry stains resulted in improved ability to classify these often devastating tumors. The understanding of molecular markers in central nervous system tumors has improved substantially in recent decades. Demonstration of specific genetic changes such as mutations can have crucial impact on selection of therapy. Genetic changes also play an increasingly important role when it comes to classification of these tumors. Correct classification and grading are important to be able to give correct prognostic and predictive information and are of fundamental importance for efficient clinical patient handling. In this thesis, we use several molecular techniques to improve tumor diagnosis and tumor classification and investigate the utility of these methods to give a deeper understanding of these neoplastic processes.

In **Paper I**, we investigated the DNA methylation profiling method for molecular classification of diffuse lower grade gliomas. We showed that DNA methylation profiling not only gave correct diagnostic and prognostic information but also were able to give reliable molecular information enabling molecular classification of the tumors according to the World Health Organization classification system.

In **Paper II**, we assessed changes in DNA methylation pattern over time in diffuse *IDH*-mutant gliomas. We showed that tumors accumulated methylation alterations during progression, but that the overall methylation patterns most often were maintained upon recurrence.

In **Paper III**, we explored if a proposed immunohistochemistry-based investigation of phenotype predicted survival and tumor recurrence in a clinical cohort of diffuse low-grade gliomas that were reclassified according to the 2021 WHO criteria.

In **Paper IV**, we describe a 16-month-old patient with a tumor in the third ventricle with a relapse two years after diagnosis. The tumor was initially classified as a low-grade glioma but was after methylation profiling reclassified as an infant-type hemispheric glioma. To search for druggable targets and for further refinement of the molecular background both whole genome sequencing and whole transcriptome sequencing were performed. A novel *TPR::ROS1* fusion gene was detected activating the *MAPK*-, *PI3K*- and *JAK/STAT*- pathways.

In **Paper V**, we present a cystic pilocytic astrocytoma with *KIAA1549::BRAF* fusion in a 16-year-old patient. The tumor showed ganglion cell morphology and different vascularization in a nodular component. With extended molecular examination we were able to prove that the cells with ganglion cell morphology were of neoplastic origin.

In conclusion, we further demonstrate the importance of adding molecular investigation in the histopathological diagnostic work-up. We also present arguments for the importance of evaluating molecular findings in correlation with the histomorphology picture.

Keywords: Histopathology, DNA methylation profiling, DNA methylation-based classification, Diffuse lower grade-glioma, Genomic analysis, Molecular biomarkers, Pediatric glioma

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