

BRAIN TUMORS IN CHILDREN

National population-based studies on classification, diagnostics and long-term follow-up

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i föreläsningssal Tallen, Drottning Silvias barn-och ungdomssjukhus, den 26 maj 2023, klockan 9.00

av **Elizabeth Habib Schepke**

Fakultetsopponent:

Associate Professor David Scheie, University of Copenhagen, Denmark

Avhandlingen baseras på följande delarbeten

- I. Schepke E, Lannering B, Lähteenmäki P, Georgantzi K, Sandström P-E, Nyman P, Eliasson-Hofvander M, Öberg A, Carén H, Sabel M. Incidence and long-term survival in children diagnosed with CNS tumors in Sweden 1984-2021. *Manuscript*.
- II. Schepke E, Löfgren M, Pietsch T, Olsson Bontell T, Kling T, Wenger A, Ferreyra Vega S, Danielsson A, Dosa S, Holm S, Öberg A, Nyman P, Eliasson-Hofvander M, Sandström P-E, Pfister S M, Lannering B, Sabel M, Carén H. DNA methylation profiling improves routine diagnosis of paediatric central nervous system tumours: A prospective population-based study. *Neuropathol Appl Neurobiol*, 2022, 48(6).
- III. Schepke E, Löfgren M, Pietsch T, Kling T, Nordborg C, Olsson Bontell T, Holm S, Öberg A, Nyman P, Eliasson-Hofvander M, Sabel M, Lannering B, Carén H. Supratentorial CNS-PNETs in children; a Swedish population-based study with molecular re-evaluation and long-term follow-up. *Clinical Epigenetics*, 2023, 15(1):40.

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Abstract

Although the prognosis for pediatric tumors of the central nervous system (CNS) has improved over time it is urgent to reduce mortality and improve long-term quality of life for survivors. With this aim, the first step is to identify the correct diagnosis in order to choose the right therapy and avoid unnecessary treatment. Establishing a correct diagnosis can be challenging and genome-wide DNA methylation profiling has evolved as a valuable tool in the diagnostics of childhood CNS tumors. The aim of this thesis was 1) to provide comprehensive data on children diagnosed with a CNS tumor in Sweden between 1984-2021, and 2) to evaluate the added value of performing DNA methylation profiling in the standard diagnostics of pediatric CNS tumors in Sweden.

In Paper I we found a stable incidence of childhood CNS tumors during the study period of almost 40 years. The distribution of tumor diagnoses was relatively comparable to that reported from other countries. Overall survival for children diagnosed with a CNS tumor has improved over time but for several tumor types the long-term survival rates continued to decrease.

In paper II we determined that integrating DNA methylation profiling into real time diagnostics of pediatric CNS tumors improves diagnostics and provides molecular information that has shown to be essential for choosing the optimal treatment. We demonstrated that methylation profiling has a role in the classification of all types of CNS tumors, also those with a lower tumor cell content.

In paper III we re-classified tumors formerly diagnosed as CNS primitive neuroectodermal tumor (PNET). We confirmed the heterogeneity of these tumors and concluded that DNA methylation has a pivotal role in the diagnostics of rare childhood embryonal tumors. The survival rates for the re-classified tumor types were in line with other studies. All patients with CNS NB-*FOXR2* had received craniospinal irradiation and the prognosis was excellent.

Keywords: Pediatric CNS tumors, population-based, DNA methylation, profiling, CNS-PNET, re-evaluation, incidence rate, long-term outcome, classification