UKE Paper of the Month Mai 2022

DNA Methylation subclass Receptor Tyrosine Kinase II (RTK II) is predictive for seizure development in glioblastoma patients

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Neuro-Oncology; 2022 May 2

ABSTRACT:

Background: Seizures can present at any time before or after the diagnosis of a glioma. Roughly, 25-30 % of glioblastoma (GBM) patients initially present with seizures, and an additional 30 % develop seizures during the course of the disease. Early studies failed to show an effect of general administration of anti-epileptic drugs for glioblastoma patients, since they were unable to stratify patients into high- or low-risk seizure groups.

Methods: 111 patients, who underwent surgery for a GBM, were included. Genome-wide DNA methylation profiling was performed, before methylation subclasses and copy number changes inferred from methylation data were correlated with clinical characteristics. Independently, global gene expression was analyzed in GBM methylation subclasses from TCGA datasets (n=68).

Results: Receptor tyrosine Kinase (RTK) II GBM showed a significantly higher incidence of seizures than RTK I and mesenchymal (MES) GBM ($p<0.01$). Accordingly, RNA expression datasets revealed an upregulation of genes involved in neurotransmitter synapses and vesicle transport in RTK II glioblastomas. In a multivariate analysis, temporal location ($p=0.02$, OR 5.69) and RTK II ($p=0.03$, OR 5.01) were most predictive for preoperative seizures. During postoperative follow-up, only RTK II remained significantly associated with the development of seizures ($p<0.01$, OR 8.23). Consequently, the need for antiepileptic medication and its increase due to treatment failure was highly associated with the RTK II methylation subclass ($p<0.01$).

Conclusion: Our study shows a strong correlation of RTK II glioblastomas with preoperative and long-term seizures. These results underline the benefit of molecular glioblastoma profiling with important implications for postoperative seizure control.

STATEMENT:

This project exemplifies the role of DNA methylation based subclassification with a strong clinical implication. Furthermore, it shows the strong neuro-oncology potential at the UKE.

BACKGROUND:

Both first authors have strong research interests in the field of neurooncology and are working on the clinical feasibility of epigenetic subclassification of brain tumors